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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61F 13/02</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 90/10425</b> <b>(43) International Publication Date:</b> 20 September 1990 (20.09.90)
<b>(21) International Application Number:</b> PCT/US90/01273 <b>(22) International Filing Date:</b> 8 March 1990 (08.03.90)  <b>(30) Priority data:</b> 320,570 8 March 1989 (08.03.89) US  <b>(71) Applicant:</b> RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY [US/US]; Old Queens Building, Somerset and George Streets, New Brunswick, NJ 08903 (US).  <b>(72) Inventors:</b> CHIEN, Yie, W. ; 5 West Lake Court, North Brunswick, NJ 08902 (US). CHIEN, Te-Yen ; 10 Quail Court, Branchburg, NJ 08876 (US).		<b>(74) Agent:</b> SINN, Leroy, G.; P.O. Box 559, Oldwick, NJ 08858 (US).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> TRANSDERMAL ABSORPTION DOSAGE UNIT FOR POSTMENOPAUSAL SYNDROME TREATMENT AND PROCESS FOR ADMINISTRATION  <b>(57) Abstract</b> <p>Transdermal absorption dosage units have been developed for treatment of postmenopausal syndrome which comprise a backing layer, an adjoining adhesive polymer layer in which at least minimum effective daily doses of an estrogen is microdispersed. Presently preferred is use of the natural estrogen, 17-<i>beta</i>-estradiol, or ethinyl estradiol or combinations thereof together with an amount of a natural progestogen or a progestin to minimize any potential side effects. The units use bioacceptable adhesive and polymers. An additional polymer layer in intimate contact with the estrogen-containing layer can be used. Also, a separating layer can optionally be used in making the dosage units, which separate the two adhesive polymer layers, which permits estrogen transmission from the first adhesive polymer layer during treatment. Dosage units are provided which transdermally deliver at least minimum daily doses of the estrogen for at least one day or for multiple days, such as for one week. The invention also provides a process for postmenopausal syndrome treatment using the novel dosage units.</p>		

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TRANSDERMAL ABSORPTION DOSAGE UNIT  
FOR POSTMENOPAUSAL SYNDROME TREATMENT  
AND PROCESS FOR ADMINISTRATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 06/868,709, filed May 30, 1986.

TECHNICAL FIELD

This invention relates to a novel transdermal absorption dosage unit adapted for postmenopausal syndrome treatment comprising a backing layer and an adjoining layer of a biologically acceptable adhesive polymer in which estradiol or another steroidal pharmaceutical having estrogenic activity is microdispersed in microreservoirs formed of selected transdermal absorption enhancing agents. The adhesive layer provides the means by which the dosage unit adheres to the skin of the subject being administered said estrogenic pharmaceutical and permits transdermal absorption of said estrogenic pharmaceutical. An amount of a progestin can also be incorporated into the adhesive polymer layer to diminish any side effects encountered in postmenopausal syndrome treatment. Additionally, the invention relates to an improved process for administration in postmenopausal syndrome treatment.

5           BACKGROUND ART

10           It has been found that certain pharmaceuticals are  
15           absorbed to a degree through the skin. This is referred to  
20           as transdermal pharmaceutical absorption. One means of  
25           effecting transdermal absorption has been to distribute the  
30           pharmaceutical within a polymeric disc or a container of a  
35           gel, which is brought into contact with an area of the skin  
40           of the subject to be treated with the pharmaceutical. Also,  
45           ointments or lotions containing a desired pharmaceutical  
            have been applied to an area of the skin of the subject to  
            be treated. Problems encountered in such treatment include  
            inadequate control over the rate and duration of transdermal  
            absorption or the rate can be too slow in the case of cer-  
            tain dosage forms, especially from pharmaceutical-containing  
            discs or pharmaceutical-containing gel container dosage  
            units or pads. It has been found that the transdermal  
            absorption rates of certain pharmaceuticals can be increased  
            by use of transdermal absorption enhancing agents with the  
            pharmaceutical to be absorbed when compounding the polymeric  
            disc or the pharmaceutical-containing gel.

50           It is desired to improve the dosage unit forms or  
55           devices by which pharmaceuticals are transdermally absorbed,  
            especially in view of the importance of administration of  
            pharmaceuticals by this means. Desired transdermal absorp-  
            tion of pharmaceuticals would provide an avoidance of gas-  
            trointestinal incompatibility with the pharmaceuticals and  
            unwanted destruction of the pharmaceutical by metabolism in

5 the gastrointestinal tract and by a "first pass" hepatic  
metabolism. The transdermal absorption minimizes inter- and  
10 intra-patient variations regarding such incompatibilities  
and metabolisms. By transdermal absorption, it is deemed  
15 possible to provide more constant pharmaceutical concentra-  
tion in the body and to realize a greater pharmaceutical  
efficiency. It is possible, by proper transdermal absorp-  
20 tion, to reduce the frequency of effective dosing. Trans-  
dermal administration provides most of the advantages of  
25 intravenous dosing without the necessity of hospitalization  
and the accompanying discomfort and inconvenience.

30 The estrogenic steroid estradiol is an illustration of  
a pharmaceutical in which great loss of orally administered  
estrogen occurs by first-pass through the liver, it being  
35 almost completely metabolized. Therefore, oral administra-  
tion of estradiol is not a satisfactory means of replacing  
normal levels of estradiol. It has been found that by  
40 transdermal administration, estradiol can be provided, in  
only a fraction of the amount required in oral dosing, to  
45 achieve adequate levels of estradiol, which the body for one  
or more reasons is not naturally producing to provide ade-  
50 quate levels in women to prevent body conditions and symp-  
toms caused by such inadequate levels. Also, by transdermal  
administration of estradiol, for example, the unwanted  
55 estradiol metabolites produced by first-pass hepatic metabo-  
lism are greatly reduced. An additional advantage of trans-

5 dermal administration is the attainment of more constant levels of estradiol and other estrogenic steroids.

10 The need for estradiol replacement therapy is caused by menopause (the cessation of ovarian function), oophorectomy  
15 (loss of one or both ovaries by surgery) or by pituitary failure. Replacement estrogenic therapy is an important need. Besides the need to alleviate the menopausal symptoms  
20 caused by estrogenic steroid deficiency, there are additional contributions of such replacement estrogenic therapy associated with osteoporosis (loss of bone mass) and athero-  
25 sclerosis. There is clearly a need for improvements in means and methods for postmenopausal syndrome and other estrogenic steroid therapy. Even though it has been found  
30 that estradiol itself or estradiol in the form of certain derivatives such as mono- or di-esters (e.g., acetate esters) can be absorbed transdermally, it is desired that  
35 improved transdermal estradiol and other estrogenic steroid absorption dosage unit forms and processes of transdermal administration be developed. A number of benefits would  
40 result.  
45

#### SUMMARY OF INVENTION

50 This invention relates to a transdermal dosage unit for treatment of postmenopausal syndrome having the following:

- 55 a) a backing layer which is substantially impervious to an effective estrogen to be delivered transdermally from the adhesive polymer disc layer and any

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other components of the adhesive polymer disc layer; and

- b) an adhesive layer which is adhered to said backing layer and which had dispersed therein in micro-reservoirs an effective amount of an estrogen effective in treatment of postmenopausal syndrome, said adhesive polymers being biocompatible, compatible with said estrogen and permitting said estrogen to be transdermally absorbed; said adhesive polymer disc layer having one or more transdermal absorption enhancing agents microdispersed therein, said transdermal absorption agent or agents selected from biocompatible compounds having at least six carbon atoms and which are capable of forming microreservoirs during microdispersion with said adhesive polymer and estrogen to encapsulate said estrogen in said adhesive polymer used to make said adhesive polymer disc layer and being substantially insoluble or insoluble in water;

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said dosage unit capable of delivering a dosage amount of said estrogen for at least seven successive days.

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The microreservoirs suitably have diameters in the range of from about 1 to about 150 microns and desirably from about 2 to about 10 microns. It is understood that some minor amount by weight of the transdermal absorption

5 enhancing agent component can be present in microreservoirs  
having diameters somewhat lesser or greater than the above  
10 referred to ranges so long as the effectiveness of the  
dosage units provided by this invention is retained.

15 The adhesive polymer layer also adheres the dosage unit  
in intimate contact with the skin of the subject being  
treated to permit the estrogen to be absorbed transdermally.

20 Optionally, an additional adhesive layer can be formed  
using the same or a different adhesive polymer which is also  
25 biocompatible and placed in intimate contact with the sur-  
face of the estrogen-containing adhesive polymer layer con-  
taining the estrogen steroid. This adhesive layer can con-  
30 tain one or more effective transdermal absorption enhancing  
agents or be free of these agents.

35 Optionally, another layer can be included in the dosage  
units between the estrogen-containing adhesive polymer layer  
and the adhesive layer which has present an effective amount  
40 of one or more enhancing agents. In this separating layer,  
it is preferable to have present little or no estrogen,  
45 progestin or enhancing agents. The separating layer can be  
made using adhesive polymers such as used in making the  
estrogen-containing adhesive polymer layer, for example,  
50 with a bioacceptable polyisobutylene or polyacrylic adhe-  
sive, which permits the estrogen in the layer to be trans-  
mitted for transdermal absorption being presently preferred.  
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5           Additionally, it is presently preferred that the separating  
layer be free of any substantial amount of transdermal  
10       absorption enhancing agent.

          The estrogen-containing adhesive polymer layer can  
alternatively be made with the estrogen such as estradiol  
15       present in microdispersed form without substantial use of  
the transdermal absorption enhancing agents described above.

20           The backing layer is made from materials that are sub-  
stantially impermeable with regard to the pharmaceuticals of  
the transdermal dosage unit. It can be made of polymers  
25       such as polyethylene, polypropylene, polyvinylchloride,  
polyesters such as poly(ethylene phthalate), and foils such  
30       as laminates of polymer films with metallic foils such as  
aluminum foil.

35           The estrogen-containing adhesive layer is suitably  
fabricated from biologically acceptable adhesive polymers,  
such as a suitable polyacrylic adhesive polymers, silicone  
40       adhesive polymer or a polyisobutylene adhesive. The estro-  
gen is suitably dispersed in the adhesive polymer. For  
45       example, it has been found suitable to form a mixture with a  
biocompatible, liquid transdermal absorption enhancing  
agent. It has been found in many cases that certain  
50       straight-chain saturated alkanols, such as n-decyl alcohol,  
work in a satisfactory manner in the mixture of estrogen and  
adhesive polymer. The adhesive polymer is added to the  
55       mixture of estrogen and n-decyl alcohol and the resulting  
combination is mixed and dispersed thoroughly. The estro-

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gen-adhesive polymer mixture is applied as a thin layer to the backing layer and is dried. Care must be taken that the adhesive polymer selected is compatible with the estrogen and other active pharmaceuticals, permits their release for transdermal absorption and is free or sufficiently free from any biologically unacceptable components.

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A suitable derivative of estradiol or other estrogenic steroids used in formulating the polymer matrix disc layer is commonly an ester which is biologically compatible and can be absorbed effectively transdermally. Also, it is ordinarily desired that such esters are bioconvertible by components of the skin or other portions of the body such as hydrolytical enzymes (e.g., esterase) to estradiol or other desired estrogenic steroid. If the derivative is an ester, the derivative can be a mono- or di-ester if the estrogenic steroid has two esterifiable groups. In the case of estradiol, it has hydroxy groups at the 3- and 17- positions and therefore the 3-mono and 17-mono as well as the 3,17 di-esters can be made by generally known esterification methods. Some ester derivatives will be absorbed more readily than the basic estradiol or other estrogenic steroid. In selection of ester derivatives, it is ordinarily preferred that the ester derivative be absorbed more effectively than the basic compound and bioconverts efficiently, after absorption, to estradiol or other basic estrogenic steroid used. Valerate mono- and di-esters of

5 estradiol are presently considered to be desirable esters.  
In formulating the adhesive layer, it is desirable at times  
10 to utilize two or more pharmaceuticals, such as the combina-  
tion of a estradiol ester, like estradiol valerate, with an  
15 amount of estradiol. Also, one estrogenic steroid either in  
the form of the basic compound or derivative such as a bio-  
convertible ester, or combinations thereof, can be combined  
20 with another steroid which has a different efficacy, such as  
a progestogen or a synthetic progestin, in a suitable amount  
25 in order to minimize potential side effect of the estrogenic  
postmenopausal syndrome therapy.

It has been found suitable to add the natural progesto-  
30 gen, progesterone, or a synthetic progestin, such as levo-  
norgestrel, in an appropriate amount to the estrogen-adhe-  
sive mixture used in making the adhesive layer.  
35

It has further been found to be advantageous to add  
effective amounts of selected surfactants, such as biocom-  
40 patible non-ionic surfactants sold under the designations  
Tween 20 and Tween 60, to the combination of estrogen such  
45 as estradiol and transdermal absorption enhancing agent,  
such as n-decyl alcohol. The amount of such surfactant used  
can vary. However, an amount of such surfactant in the  
50 range of 0.25 to 1 part based on 100 parts of the final  
estrogen-adhesive mixture used to form the adhesive layer  
55 has been found satisfactory.

5           The adhesive polymer layers can be formed by spraying  
or by solvent casting or laminating. The concentration of  
10   transdermal absorption enhancing agent, if employed, can be  
reduced in the portion of the adhesive polymer layer means,  
15   especially if less than desired adhesion is realized in the  
adhesive layer, by applying the surface portion of the adhe-  
sive layer separately wherein the adhesive composition has a  
20   lower concentration of transdermal absorption enhancing  
agent. The adhesive polymer layer is desirably thin in the  
micron-range thickness, suitably 10-200 microns in thick-  
25   ness, desirably about 20 to 180 microns, and preferably  
about 30 to 150 microns in thickness.

30           The absorption rate of the transdermal pharmaceutical  
absorption dosage units of the invention can be increased,  
such as by having an Enhancing Factor of at least 1.2,  
35   preferably at least 1.3, and more preferably at least about  
1.5. Enhancing Factor is defined as the ratio of normalized  
40   permeation rate [in mcg/cm<sup>2</sup>/hr] of a dosage unit of this  
invention with transdermal absorption enhancing agent/the  
normalized permeation rate of a corresponding dosage unit  
45   without enhancer.

50           The invention also is a process for administering said  
estrogen with or without added natural progestogen or syn-  
thetic progestin by applying said dosage unit to the skin of  
the subject to be treated, whereby said pharmaceuticals are  
55   transdermally administered to said subject to treat menopau-  
sal syndrome.

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BRIEF DESCRIPTION OF THE DRAWINGS

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FIG. 1 is a graph showing the enhancing effect of alkanolic acid in a dosage unit on the human cadaver skin permeation rate of estradiol.

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FIG. 2 is a graph showing the enhancing effect of alkanol in a dosage unit on the human cadaver skin permeation rate of estradiol as a function of alkyl chain length.

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FIG. 3 is a graph showing the effect of concentration of n-decyl alcohol in a dosage unit on the human cadaver skin permeation rate of estradiol.

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FIG. 4 is a graph showing the effect of drug loading in a dosage unit on the human cadaver skin permeation rate of estradiol.

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FIG. 5 is a graph showing the effect of thickness of coating in a dosage unit on the human cadaver skin permeation rate of estradiol.

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FIG. 6 is a graph showing estradiol skin permeation rates from dosage unit stability samples.

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FIG. 7 is a graph comparing human cadaver skin permeation profiles of estradiol absorbed from the Rutgers dosage units as compared to Estraderm TTS-50.

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FIG. 8 is a graph showing the enhancing effect of alkanols in a dosage unit on the human cadaver skin permeation rate of ethinyl estradiol as a function of alkyl chain length.

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FIG. 9 is a graph showing the effect of concentration of n-decyl alcohol in a dosage unit on the human cadaver skin permeation rate of ethinyl estradiol.

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FIG. 10 is a graph showing the effect of drug loading in a dosage unit on the human cadaver skin permeation rate of ethinyl estradiol.

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FIG. 11 is a graph of ethinyl estradiol skin permeation rates from dosage unit stability samples.

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FIG. 12 is a graph showing, in a dosage unit, the effect of thickness of an adhesive polymer layer separating the adhesive polymer drug reservoir layer and an enhancer-containing adhesive polymer layer designed for contact with skin of subject.

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FIG. 13 is a graph showing the effect of the chain length of alkanols as enhancer in a dosage unit on the human cadaver skin permeation rate of estradiol.

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FIG. 14 is a graph showing the effect of estradiol loading dose in the reservoir adhesive polymer layer of a dosage unit on the human cadaver skin permeation rate of estradiol.

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FIG. 15 is a graph showing the effect of the thickness of enhancer-containing upper layer in a dosage unit on the human cadaver skin permeation rate of estradiol.

55  
FIG. 16 is a graph showing the effect of concentration of n-decyl alcohol in the upper layer of a dosage unit on the human cadaver skin permeation rate of estradiol.

5           FIG. 17 is a graph comparing human cadaver skin permea-  
tion profiles of estradiol from a Rutgers tri-layer dosage  
10 unit as compared to Estraderm.

15           FIG. 18 is a photomicrograph at 635x magnification of a  
section of an adhesive polymer drug reservoir layer showing  
transdermal absorption enhancer microreservoirs containing  
20 drug (estradiol).

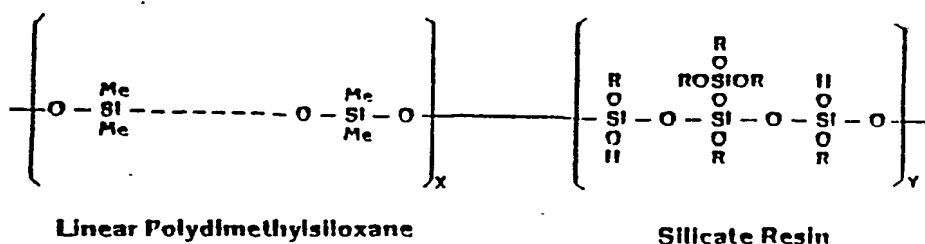
25           DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED  
EMBODIMENTS

30           The backing layer can be made of any suitable material  
which is impermeable to the pharmaceuticals dispersed within  
the adjacent adhesive polymer layer. The backing layer  
serves as a protective cover for the estrogen-containing  
35 adhesive layer and provides also a support function. The  
backing can be formed so that it is essentially the same  
size layer as the estrogen-containing adhesive layer or it  
40 can be of larger dimension so that it can extend beyond the  
side of the estrogen-containing adhesive layer or overlay  
45 the side or sides of the estrogen-containing adhesive layer  
and then can extend outwardly in a manner that the surface  
of the extension of the backing layer can be a base for an  
50 adhesive to hold the dosage unit in intimate contact with  
the skin of the subject treated.

55           Examples of materials suitable for making the backing  
layer are films of high and low density polyethylene, poly-  
propylene, polyvinylchloride, polyesters such as poly(ethy-

lene phthalate), metal foils, metal foil laminates of such suitable polymer films, and the like. Preferably, the materials used for the backing layer are laminates of such polymer films with a metal foil such as aluminum foil. In such laminates, a polymer film of the laminate will usually be in contact with the polymer matrix layer. The backing layer can be any appropriate thickness which will provide the desired protective and support functions. A suitable thickness will be from about 10 to about 200 microns. Desirably, the thickness will be from about 15 to about 150 microns, and preferably be from about 20 to about 100 microns.

The adhesive layers are suitably made using a silicone based pressure sensitive adhesive, such as a (polydimethylsiloxane-silicate resin) copolymer adhesive depicted by the following formula:

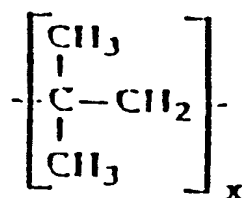


wherein Me is methyl and R is  $-\text{Si}(\text{CH}_3)_3$  and x and y represent independent numbers of repeating units sufficient to provide the desired properties in the adhesive polymer and other polymer layers.

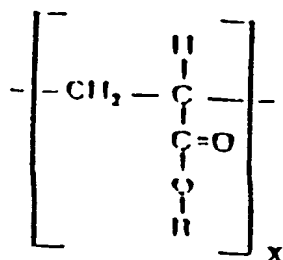


For example, adhesive polymer products or amine-resistant adhesive polymer products sold by Dow Corning, such as the ones sold under the designations of DC-355, Bio-PSA and X7-2920 medical adhesives, are suitable for use in making the adhesive layer. The adhesive polymer must be biologically acceptable and chemically compatible with the pharmaceuticals and the transdermal absorption enhancing agents. Certain polyacrylic adhesive polymers in the form of an alkyl ester, amide, free acid, or the like or polyisobutylene adhesive polymers can also be used with some pharmaceuticals utilized in the dosage units. Illustrative of suitable adhesive polymers for use in making the adhesive polymer layer are shown by the following formulas:

Polyisobutylene Adhesive



Polyacrylic Adhesive



5 wherein x represents the number of repeating units suffi-  
10 cient to provide the desired properties in the adhesive  
polymer and R is H or lower alkyl including ethyl, butyl and  
2-ethylhexyl.

15 Other suitable hypoallergenic pressure-sensitive con-  
tact adhesive compositions can also be used. A preferred  
20 adhesive layer is pressure sensitive.

25 The adhesive means then is finally covered in conven-  
tional therapeutic practice with a releasable protective  
film layer which is made from materials which are substan-  
30 tially impermeable to the pharmaceutical, the transdermal  
absorption enhancing agent and any other components of the  
dosage unit. The polymer materials and metal foil laminates  
used for the backing layer can be used to make the protec-  
35 tive layer, provided the layer is made strippable or  
releasable such as by applying conventional siliconizing. A  
suitable releasable material for use with silicone polymer  
40 adhesive DC-355 and X7-2970 is Scotch Pak 1022 material sold  
by the 3M Company or Bio-Release material sold by Dow Corn-  
45 ing.

50 In making the dosage units, the estrogen-containing  
adhesive layer can be made by dispersing an amount of estro-  
diol crystals in an adhesive solution. For example, two  
parts of estradiol crystals can be added and dispersed in 98  
55 parts of a biocompatible polyacrylate solution such as sold  
under the designation Duro-Tak 80-1054 by National Starch

5 and Chemical Co. (has about 36% w/w of solid adhesive). An  
airtight container can be used for the mixing. The mixture  
10 can be made homogeneous by gently rotating the container.

The estradiol-containing mixture can then be readily  
15 coated onto a drug-impermeable backing layer such as a composite sold under the designation Scotch Pak 1109 by 3M Company. Coating equipment unit can be used to coat the  
20 backing layer to a desired thickness. A coater found satisfactory has been a Werner Mathis Laboratory Coater Type LTSV with built-in Laboratory drier LTF. The thickness of the  
25 estradiol-adhesive layer can be accurately controlled to a desired thickness, such as to 400 microns, using such a  
30 designed coater-drier.

If desired, an amount of a material progestogen can be  
35 added to the above mixture of estradiol and adhesive solution. The amount added will depend upon the amount desired in the estradiol-containing layer. The progestogen can be  
40 progesterone or other suitable compound within the class.

45 Instead of a natural progestogen, a synthetic progestin can be incorporated into the estradiol-adhesive solution prior to its use in coating.

50 The amount of the progestogen or progestin will depend on the estrogen used and the amount desired to diminish any toxic side effects. It has been found suitable, for  
55 example, to use about 1.0 to about 10 parts of progesterone per part of estradiol or about 0.5 to about 5 parts of a progestin such as levonorgestrel per part of estradiol used.

5  
10 If another estrogen is used, the amount of progestogen or progestin will be adjusted as necessary to provide a proper amount of the progestogen or progestin per part of estrogen.

15 Additionally, an effective amount of a transdermal absorption enhancing agent can be incorporated into the estradiol-adhesive solution used in the coating process.  
20 The enhancing agent suitably is biocompatible and chemically compatible with the drugs used. A suitable enhancing agent for this use has been found to be n-decyl alcohol, a liquid  
25 enhancing agent that is not removed in the normal coating and drying procedure for forming the estradiol-adhesive layer. If n-decyl alcohol is used as the enhancing agent,  
30 the amount can be varied depending upon the enhancement desired, the drugs used, and other factors. Ordinarily, a  
35 suitable amount can be selected from a range of about 1 part to 25 parts based on 100 parts of the adhesive polymer weight.

40 Other enhancing agents can be used instead of n-decyl alcohol. Other suitable agents have been found to be n-  
45 octanol, lauryl alcohol, caprylic acid, capric acid, and lauric acid. Other suitable agents will be suggested to those having skill in art in view of the disclosures hereof.

50 The estradiol-adhesive layer can be either covered with a suitable release liner (a poly(ethylene phthalate) lami-  
55 nated with aluminum foil) or a Teflon-coated polyester film such as sold under the designation Scotch-Pak 1022 (by 3M)

5 or Bio-release X7-2741 or X7-2752 (by Dow Corning). The  
poly(ethylene phthalate) side to which the adhesive-  
10 enhancer-progestin coating is applied, is made strippable by  
conventional siliconizing or by other suitable means. The  
15 thickness of the adhesive-enhancer-progestin layer normally  
is suitably about 20 to about 1000 microns, preferably about  
50 to about 500 microns.

20 Alternatively, the estradiol-adhesive layer can be  
covered with an adhesive layer which contains an amount of  
an enhancing agent. The additional adhesive layer is made  
25 as by dissolving the enhancing agent in the adhesive polymer  
solution or in a solvent which is compatible with the adhe-  
sive polymer solution used to make the adhesive layer con-  
30 taining the transdermal absorption enhancing agent. Any  
suitable amount of solvent can be used as necessary to dis-  
35 solve the quantity of enhancer to be admixed with the adhe-  
sive polymer solution used. For example, 1 to 5 parts of  
40 solvent can be used to dissolve one part of transdermal  
absorption enhancing agent, depending upon the solubility of  
45 the enhancer. When using silicone-based adhesive solution,  
it has been found suitable to use 2 to 20 parts of trans-  
dermal absorption enhancing agent in 20 to 50 parts of sol-  
50 vent (such as acetone, methylene chloride, diethyl ether,  
methyl ethyl ketone, trifluorotrichloroethane or other suit-  
55 able solvent) and add the solution to 100 parts of the adhe-  
sive solution. The enhancer-adhesive combination is  
thoroughly mixed and a coating thereof is applied using a

5  
10 film coating machine, such as referred to in the art as a  
coater equipped with K-bar or doctor blade, directly onto  
the estradiol-adhesive layer or to a strippable release  
15 liner and dried before laminating onto the polymer layer, as  
described above.

20 The amount of enhancer in the adhesive layer depends in  
part on the rapidity at which it is desired that the hor-  
mones be absorbed. Generally speaking, about 1 to about 40  
percent of transdermal absorption permeation enhancer based  
25 on the weight of the adhesive is suitable, depending upon  
the enhancer, adhesive polymer, desired adhesiveness and  
other factors. Desirably, about 5 to about 30 percent of  
30 transdermal absorption enhancing agents are used depending  
upon the above recited factors. The adhesive layer contain-  
35 ing the transdermal absorption enhancing agent is trans-  
ferred to the estrogen-containing adhesive polymer layer  
surfaces by application of lamination technique under a  
40 constant pressure. In order to assure adequate adhesion of  
the adhesive polymer layer to the skin of the subject  
45 treated, additional adhesive polymer coating having a rela-  
tively low concentration of enhancer e.g., 1-20 percent  
based on the weight of the adhesive polymer can be further  
50 applied to the surface of enhancer-polymer layer. The  
thickness of this coating ordinarily is a minor percentage  
55 of the thickness of the final adhesive layer, such as 20-40  
percent of the total adhesive polymer layer. The solvent of

5 the respective coatings is removed by evaporation through a  
suitable drying process. The respective coatings can be  
10 combined to make the final multi-layer dosage form by appli-  
cation of lamination technique under a constant pressure or  
sequential solvent casting technique.

15 An optional separating layer can also be used and made  
of the adhesive materials. In making the separating layer,  
20 it has been found suitable to use a bioacceptable polyiso-  
butylene having a suitable molecular weight. For example,  
25 the polyisobutylene used can suitably have a relative mole-  
cular mass  $M_v$  (viscosity average) of from about 400,000 to  
about 1,700,000, such as that of polyisobutylene sold by  
30 BASF under the designation Oppanol. One particular grade,  
B80, which has a relative molecular mass  $M_v$  (viscosity  
35 average) value of 850,000, is particularly suitable in  
making the separating layer. The viscosity average relative  
molecular mass is obtained from the equation:  $J_0 = 3.06 \times 10^{-2}$   
40  $\times M_v^{0.65}$ . The viscosity or molecular weight should, gen-  
erally speaking, be selected which is sufficiently high to  
45 provide a separating layer which is dimensionally stable and  
which is not excessively high so as to make fabrication of  
the separating layer unnecessarily difficult to provide a  
50 functional and pharmaceutically elegant dosage unit.

55 The thickness of the separating layer can vary as  
desired. However, it has been found that a coating layer  
with thickness (after removal of solvent) of about 30 to  
about 500 microns to be suitable, with a thickness of about

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50 to 250 microns to be preferable. It has been found that a separating layer having about 100 micron thickness made of a polyisobutylene having a viscosity or molecular weight such as that of Oppanol B80 to function well, if the estrogen in the polymer layer is 17-beta-estradiol or ethinyl estradiol.

The separating layer should have sufficient thickness to minimize any migration, especially under prolonged storage conditions at elevated temperatures, such as 37°C or 45°C or greater. Also, the separating layer should be made of a suitable material and with a sufficient thickness to decelerate the rate of transmission of the estrogen in the adhesive polymer layer, as needed to provide a suitable delivery rate.

It has been found that the polymer solution of the separating layer can be made as by dissolving about 5 parts to about 20 parts, preferably at 10 parts of a suitable polyisobutylene, such as Oppanol B80 polyisobutylene in a suitable solvent, such as a mixture of cyclohexane, hexane and heptane (for example, a 1:1:1 mixture). The mixture is gently agitated such as by using a suitable rotator.

When the dissolution is substantially completed to provide a clear polyisobutylene solution, the solution can be used to coat onto a low adhesion film, such as a polyester film with a fluoropolymer-coated surface, for example, the material sold by 3M Company under the designation Scotch



5           Pak 1022. A R.D. wireless coating bar (such as a #12) or  
laboratory coater Type LTSV by Werner Mathis can be used for  
10       coating. The resulting coating is dried and is repeated as  
necessary to obtain a layer of desired thickness, such as  
15       100 microns. The separating layer thus formed can be  
assembled into the dosage unit by lamination to the polymer  
layer. Alternatively, the separating layer can be applied  
20       to the surface of the upper adhesive layer before being  
assembled by lamination to the surface of the lower adhesive  
polymer layer containing estrogen. The finished multi-  
25       layered adhesive polymer laminate can then be cut to form  
discs with desired shapes and sizes. The adhesive polymer  
30       layer discs generally should not exceed about 100 sq. cm in  
area, suitably about 5 to 100 sq. cm, preferably, about 8 to  
35       about 80 sq. cm, generally about 10 to 60 sq. cm being more  
preferable. The shape of the layer discs can vary; they can  
be circular, square, rectangular or other desired shape.

40           The dosage units are excised. The backing layer, if  
desired, can be shaped around the sides of the dosage unit,  
including the polymer layer, if such protection is desired.  
45       Also, a strippable layer can be placed over the face of the  
dosage unit for protection of the dosage unit. The result-  
50       ing hormone adhesive polymer dosage unit forms are then  
placed in appropriate packaging for storage until they are  
55       to be applied in transdermal treatment.

5           The following examples are in illustration of the invention and are not intended to be limiting.

10       Example 1

15           In a container, one (1) part of estradiol and 7.5 parts of progesterone were mixed with 25 parts of n-decyl alcohol to form a homogeneous dispersion. To this dispersion, 66.5 parts of polyacrylate adhesive polymer (Duro-Tak 80-1054 by National Starch and Chemical Co.) is added and the container is gently rotated to form a homogeneous mixture. This mixture is then coated onto a piece of Scotch Pak 1109 (3M Company) backing laminate by using a coating machine (Werner Mathis, Laboratory Coating Device, type LTSV). The thickness of coating is precisely set at 200 microns by the equipped micrometers on the coating machine. The coating is then dried at 50°C for 45 minutes in the dryer (Werner Mathis, type LTF). The resulted coating is allowed to cool and then is laminated with the low-adhesion side of release liner (Scotch Pak 1022, 3M Co.) by using a laminating device equipped on the coating machine. The product thus obtained is cut into dosage units of suitable size by using a die cutter. The dosage units fabricated by this procedure were found to give in-vitro human cadaver skin permeation rates of estradiol and progesterone at  $0.73 \pm 0.244$  and  $2.75 \pm 0.228$  mcg/sq. cm/hr, respectively. By comparison, the in-vitro human cadaver skin permeation rate of estradiol delivered by the marketed Estraderm TTS-50 dosage unit was found to be  $0.29 \pm 0.061$  mcg/sq. cm/hr. Therefore, at the

5 size of 10 sq. cm (the size of Estraderm TTS-50), the devel-  
10 oped transdermal dosage unit will be able to deliver pro-  
gesterone and estradiol combination at daily rates of  $660 \pm$   
54.7 and  $175.2 \pm 41.8$  micrograms, respectively for one week  
15 while Estraderm TTS-50 dosage unit can only deliver estra-  
diol alone at daily rate of  $69.6 \pm 14.6$  micrograms for 3-4  
days.

20 The transdermal dosage units of this invention are  
evaluated by using a skin specimen from a "hairless" mouse  
25 or human cadaver by following the procedure described by  
Y.W. Chien, K. Valia and M.B. Doshi in Drug Develop. & Ind.  
Pharm., 11(7) 1195-1212 (1985).

#### 30 Example 2

35 In a container, one (1) part of ethinyl estradiol and  
0.5 parts of levonorgestrel are mixed with 25 parts of n-  
decyl alcohol to form a homogeneous dispersion. To this  
40 dispersion, 73.5 parts of polyacrylate adhesive polymer  
(Duro-Talk 80-1054, by National Starch and Chemical Co.) is  
added and the container is gently rotated to form a homo-  
45 geneous mixture. This mixture is then coated onto a piece  
of Scotch Pak 1109 (3M Company) backing laminate by using a  
50 coating machine (Werner Mathis, Laboratory Coating Device,  
type LTSV). The thickness of coating is precisely set at  
200 microns by the equipped micrometers on the coating  
55 machine. The coating is then dried at  $50^{\circ}\text{C}$  for 45 minutes  
in the dryer (Werner Mathis, Laboratory Dryer, type LTF).

5 The resulted coating is allowed to cool and then laminated  
10 with the low-adhesion side of release liner (Scotch Pak  
1022, 3M Co.) by using a laminating device equipped on the  
15 coating machine. The product thus obtained is cut into  
dosage units of suitable size by using a die cutter. The  
20 dosage units fabricated by this procedure were found to give  
in-vitro human cadaver skin permeation rates of ethinyl  
estradiol and levonorgestrel at  $0.64 \pm 0.124$  and  $0.15 \pm$   
25  $0.034$  mcg/sq. cm/hr, respectively. By comparison, the in-  
vitro human cadaver skin permeation rate of estradiol  
delivered by the marketed Estraderm TTS-50 dosage unit was  
30 found to be  $0.29 \pm 0.061$  mcg/sq. cm/hr. Therefore, at the  
size of 10 sq. cm (the size of Estraderm TTS-50), the devel-  
oped transdermal dosage unit will be able to deliver levo-  
35 norgestrel and ethinyl estradiol combination at daily rates  
of  $36.0 \pm 8.16$  and  $153.6 \pm 29.76$  micrograms, respectively,  
40 for one week while Estraderm TTS-50 dosage unit can only  
deliver estradiol alone at daily rate of  $69.6 \pm 14.6$  micro-  
grams for 3-4 days.

45 The dosage units made according to the procedure of  
Example 2 have three layers in addition to the backing layer  
50 and the peelable release liner. At times herein are  
referred to as the following layers:

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      /-----  
      | release layer  
      |-----  
1 -   | adhesive layer with enhancer  
      |-----  
2 -   | separating layer  
      |-----  
3 -   | adhesive layer with estradiol  
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1 - Upper layer or adhesive layer with enhancer; 2 - Middle or separating layer; 3 - Lower or adhesive layer with estradiol.

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The following are data on dosage units made following generally the procedure of Example 2:

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Table 1: Effect of Thickness of Separating Layer on the Human Cadaver Skin Permeation Rate of Estradiol

Thickness (microns)	Human Cadaver Skin Permeation Rate of Estradiol (mcg/sq. cm/hr $\pm$ S.D. N=3)	
	Type of Estradiol Reservoir Polymer Silicone	Polyacrylate
0	0.29 (0.060)	1.08 (0.301)
50	0.17 (0.032)	0.51 (0.057)
100	0.15 (0.027)	0.34 (0.026)
200	0.14 (0.021)	0.30 (0.022)
300	0.14 (0.007)	0.27 (0.093)
400	0.10 (0.015)	0.23 (0.013)
500	0.09 (0.013)	1.08 (0.301)

Estraderm TTS-50

0.45 (0.021)

Notes:

1. Adult (65 year old) caucasian male cadaver skin was used.
2. Duration of experiment is 140 hours with 10 samples taken.
3. Separating layer made of Oppanol B80.

Table 2: Effect of Chain Length of Fatty Alcohols on the Human Cadaver Skin Permeation Rate of Estradiol

n in CH <sub>3</sub> (CH <sub>2</sub> ) <sub>n</sub> CH <sub>2</sub> OH	Estradiol Skin Permeation Rate mcg/sq. cm/hr $\pm$ S.D. N=3)
2	0.19 (0.031)
4	0.21 (0.022)
6	0.46 (0.059)
8	0.51 (0.057)
10	0.29 (0.049)
12	0.17 (0.024)
Estraderm TTS-50	0.41 (0.044)

Notes:

1. Adult (65 year old) caucasian male cadaver skin was used.
2. Duration of experiment is 122 hours with 10 samples taken.

Table 3: Effect of Estradiol Loading Dose in the Reservoir Polymer on the Human Cadaver Skin Permeation Rate of Estradiol

Loading Dose (% W/W) of Estradiol	Human Cadaver Skin Permeation Rate mcg/sq. cm/hr $\pm$ S.D. N=3)
0.10	0.04 (0.009)
0.25	0.09 (0.011)
0.50	0.16 (0.027)
1.00	0.21 (0.024)
1.50	0.42 (0.049)
2.00	0.51 (0.057)
2.50	0.50 (0.074)
Estraderm TTS-50	0.42 (0.046)

Notes:

1. Adult (65 year old) caucasian male cadaver skin was used.
2. Duration of experiment is 120 hours with 10 samples taken.



Table 4: Effect of Thickness of Enhancer-containing Upper Adhesive Layer on the Human Cadaver Skin Permeation Rate of Estradiol

Thickness (microns) of Upper Layer	Human Cadaver Skin Permeation Rate mcg/sq. cm/hr $\pm$ S.D. N=3)
100	0.21 (0.043)
200	0.40 (0.081)
300	0.52 (0.123)
400	0.51 (0.057)
500	0.42 (0.049)
600	0.31 (0.062)
700	0.26 (0.044)
Estraderm TTS-50	0.45 (0.021)

Notes:

1. Adult (65 year old) caucasian male cadaver skin was used.
2. Duration of experiment is 96 hours with 10 samples taken.

Table 5: Effect of Concentration of n-Decyl Alcohol in the Upper Adhesive Layer on the Human Cadaver Skin Permeation Rate of Estradiol

Concentration (% W/W) of n-Decyl Alcohol	Human Cadaver Skin Permeation Rate mcg/sq. cm/hr $\pm$ S.D. N=3)
0	0.03 (0.006)
10	0.10 (0.011)
15	0.25 (0.071)
20	0.52 (0.074)
25	0.69 (0.089)
30	0.89 (0.214)
Estraderm TTS-50	0.45 (0.021)

Notes:

1. Adult (65 year old) caucasian male cadaver skin was used.
2. Duration of experiment is 96 hours with 10 samples taken.

Example 3

Two (2) parts of estradiol crystals are dispersed in 98 parts of polyacrylate adhesive solution (Duro-Tak 80-1054, National Starch and Chemical Co., containing 36% W/W of solid) in an air tight container. The container is rotated at 10 rpm under ambient temperature for 10 minutes to allow gentle mixing of estradiol with the adhesive solution. A homogeneous estradiol/adhesive dispersion can be obtained in this step. This estradiol/adhesive dispersion is then coated onto a drug-impermeable backing composite (Scotch Pak 1109, 3M Co.) which is mounted on the coating frame of a laboratory coater/dryer unit (Werner Mathis Laboratory Coater Type LTSV with Laboratory Dryer LTF). The thickness of this coating is precisely controlled at 400 microns by the micrometers equipped on the coating station of this coater/dryer unit. The coating is dried at 50°C for 10 minutes in the dryer which is equipped with a sophisticated temperature and time controller. The intermediate product (1) thus formed is the estradiol-loaded reservoir lower layer as shown in Figure 1.

Ten (10) parts of polyisobutylene polymer (Oppanol B80, BASF Co.) is dissolved in 90 parts of a solvent system to form a clear polymer solution. The solvent system contains mixture of cyclohexane, n-hexane and n-heptane at 1:1:1 ratio. This polyisobutylene polymer solution is then coated onto the low-adhesion side of a release liner (Scotch Pak 1022, 3M Co.) which is mounted on the coating frame of the

5 same laboratory coater/dryer unit described in the first  
10 paragraph. The thickness of coating is 50 microns which is  
also precisely controlled by the micrometers equipped on the  
15 coating station of the coater/dryer unit. This coating is  
dried at 50°C for 5 minutes in the LTF Dryer to form the  
intermediate product (2) which contains the permeability-  
20 regulating partition separating layer of the system, as  
shown in the diagram of Example 2.

25 The intermediate product (2) is then removed from the  
coating frame and laminated onto the estradiol-loaded reser-  
voir layer of intermediate product (1) by using a laminating  
30 device equipped on the coating station of LTSV coater.  
After the lamination, the peelable release liner of inter-  
mediate product (2) is peeled off which allows the polyiso-  
35 butylene polymer coating of intermediate product (2) to be  
transferred to the estradiol-loaded reservoir layer of  
intermediate product (1). The combined structure is here-  
40 after called the intermediate product (3).

45 Twenty (20) parts of n-decyl alcohol is mixed with 80  
parts of polyacrylate adhesive solution (Duro Tak 80-1054,  
National Starch and Chemical Co., containing 36% W/W of  
50 solid) in an air-tight container. The container is rotated  
gently at 10 rpm on a rotator for 10 minutes at ambient  
temperature until a homogeneous solution is obtained. A 400  
55 microns thick of this solution is then coated onto the poly-  
isobutylene coating layer of intermediate product (3) using

5 the same LTSV Coater described in the previous paragraphs.  
The coating is dried in the LTF Oven at 50°C for 30 minutes  
10 to form the intermediate product (4).

To complete the fabrication of this tri-layer trans-  
dermal estradiol delivery system, a piece of release liner  
15 (Scotch Pak 1022, 3M Co.) is laminated, using the laminating  
device of the LTSV Coater, onto the intermediate product (4)  
20 with the low-adhesion releasing surface facing the coated  
surface of intermediate product (4). The product thus  
formed is thereafter called intermediate product (5).  
25

The intermediate product 95) can be cut into trans-  
dermal dosage units of specific size and shape by using a  
30 stainless steel die cutter. The final product of this  
fabrication process, Rutgers' tri-layer transdermal estro-  
diol delivery system, has the multilayer structure as shown  
35 in Figure 1.

Dosage units of the tri-layer transdermal estradiol  
40 delivery system thus prepared were evaluated in vitro using  
the commercially available product Estraderm TTS-50 (Ciba  
Geigy) as control. As shown in Figure 7, the Rutgers' tri-  
45 layer transdermal estradiol delivery system give slightly  
higher human cadaver skin permeation rate of estradiol than  
the Estraderm TTS-50 ( $0.51 \pm 0.057$  vs  $0.45 \pm 0.021$  mcg/sq.  
50 cm/hr, N=3). This steady state permeation rate of estradiol  
delivered from Rutgers' system was found to last for as long  
55 as 140 hours which allows this system to be used as once-a-  
week transdermal estradiol delivery system.

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WHAT IS CLAIMED IS:

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1. A transdermal dosage unit for treatment of postmenopausal syndrome having the following:

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- a) a backing layer which is substantially impervious to an effective estrogen to be delivered transdermally from the adhesive polymer layer and other components of the adhesive polymer disc layer; and
- b) an adhesive polymer layer which is adhered to said backing layer and which has dispersed therein within microreservoirs an effective daily dosage amount of an estrogen effective in treatment of postmenopausal syndrome, said adhesive polymer being biocompatible, compatible with said estrogen and permitting said estrogen to be transdermally absorbed; said adhesive polymer layer having one or more transdermal absorption enhancing agents microdispersed therein predominantly on a weight basis in the form of microreservoirs having diameters within the range of about 1 to about 150 microns, said transdermal absorption agent or agents selected from biocompatible compounds having at least six carbon atoms and which are capable of forming microreservoirs during microdispersion with said adhesive polymer and estrogen to encapsulate said estrogen in said adhesive polymer used to make said adhesive polymer layer

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5 and being substantially insoluble or insoluble in  
water;

10 said dosage unit capable of delivering to the subject  
being treated a daily estrogen dosage for at least a  
15 term of one day to about seven successive days.

2. A transdermal dosage unit of Claim 1 in which the  
20 estrogen is selected from ethinyl estradiol, 17-beta-  
estradiol, bioconvertible derivatives thereof, and  
combinations thereof.

25 3. A transdermal dosage unit of Claim 1 which has an  
effective amount of a compound selected from the group  
30 consisting of progestogens and progestins, which are  
capable of transdermal absorption, and combinations  
35 thereof.

4. A transdermal dosage unit of Claim 1 which has an  
40 effective amount of 17-beta-estradiol as said estrogen  
and an effective amount of progesterone present in said  
adhesive polymer microreservoir layer.

45 5. A transdermal dosage unit of Claim 1 in which the  
transdermal absorption enhancing agent used to provide  
50 said microreservoirs is n-decyl alcohol.

55 6. A transdermal dosage unit of Claim 1 in which the  
diameters of the microreservoirs are within the range  
of about 2 to about 100 microns.

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7. A transdermal dosage unit for treatment of postmenopausal syndrome having the following:

- a) a backing layer which is substantially impervious to an effective estrogen to be delivered transdermally from the adhesive polymer layer and other components of the adhesive polymer disc layer; and
- b) an adhesive polymer layer which is adhered to said backing layer and which has microdispersed therein an effective daily dosage amount of an estrogen effective in treatment of postmenopausal syndrome, said adhesive polymer being biocompatible, compatible with said estrogen and permitting said estrogen to be transdermally absorbed;

said dosage unit capable of delivering to the subject being treated a daily estrogen dosage for at least a term of one day to about seven successive days.

8. A transdermal dosage unit of Claim 7 in which the estrogen is selected from ethinyl estradiol, 17-beta-estradiol, bioconvertible derivatives thereof, and combinations thereof.

9. A transdermal dosage unit of Claim 7 which has an effective amount of a compound selected from the group consisting of progesterone and progestins, which are capable of transdermal absorption, and combinations thereof.



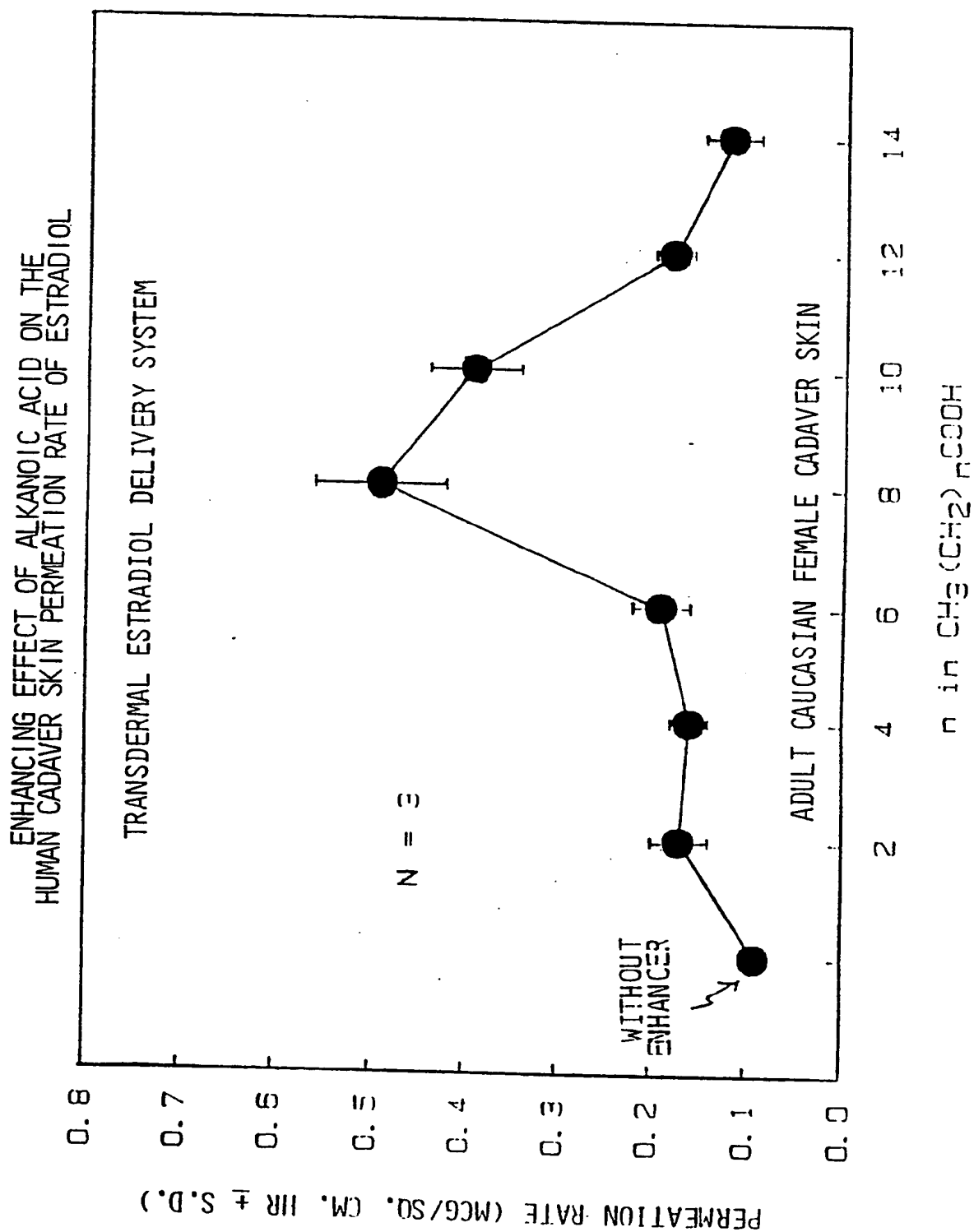
- 5
10. A transdermal dosage unit of Claim 7 which has an  
10 effective amount of 17-beta-estradiol as said estrogen  
and an effective amount of progesterone.
- 15
11. A transdermal dosage unit of Claim 7 which has an addi-  
tional adhesive polymer layer in intimate contact with  
20 said adhesive polymer layer containing estrogen which  
is made from an adhesive polymer which is substantially  
free of estrogen.
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12. A transdermal dosage unit of Claim 11 in which an  
effective amount of a transdermal absorption enhancing  
30 agent is dispersed in the additional adhesive-polymer  
layer.
- 35
13. A transdermal dosage unit of Claim 12 wherein the  
transdermal absorption enhancing agent is n-decyl alco-  
hol.
- 40
14. A transdermal dosage unit of Claim 11 wherein said  
adhesive polymer layer having present estrogen and said  
45 additional adhesive polymer layer are separated by, but  
are in respective intimate contact therewith, a biocom-  
patible adhesive polymer separating layer through which  
50 said estrogen is transmitted for desired transdermal  
absorption, said separating layer made using an adhe-  
55 sive polymer which is free or substantially free of  
estrogen, progestin and enhancing agents.

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15. A transdermal dosage unit of Claim 14 which has ethinyl estradiol or 17-beta-estradiol or combinations thereof as said estrogen component.
  16. A transdermal dosage unit of Claim 14 wherein the separating layer is made from a bioacceptable adhesive polymer having a sufficiently high viscosity or molecular weight to provide a dimensionally stable separating layer and a substantial reduction in the transmission rate of said estrogen component.
  17. A transdermal dosage unit of Claim 14 wherein the dosage unit has an effective amount of a member of the group consisting of bioacceptable progestogens and progestins, and bioconvertible derivatives thereof, which are capable of transdermal absorption.
  18. A transdermal dosage unit of Claim 16 where the separating layer is made from a polyisobutylene adhesive.
  19. A process for treating postmenopausal syndrome by applying to the skin of a subject desiring said treatment dosage units as defined in Claim 1 successively to provide effective daily dosage amounts of said estrogen for as long as said treatment is desired.

5  
20. A process for treating postmenopausal syndrome by  
applying to the skin of the subject desiring said  
10 treatment dosage units as defined in Claim 7 succes-  
sively to provide effective daily dosage amounts of  
said estrogen for as long as said treatment is desired.  
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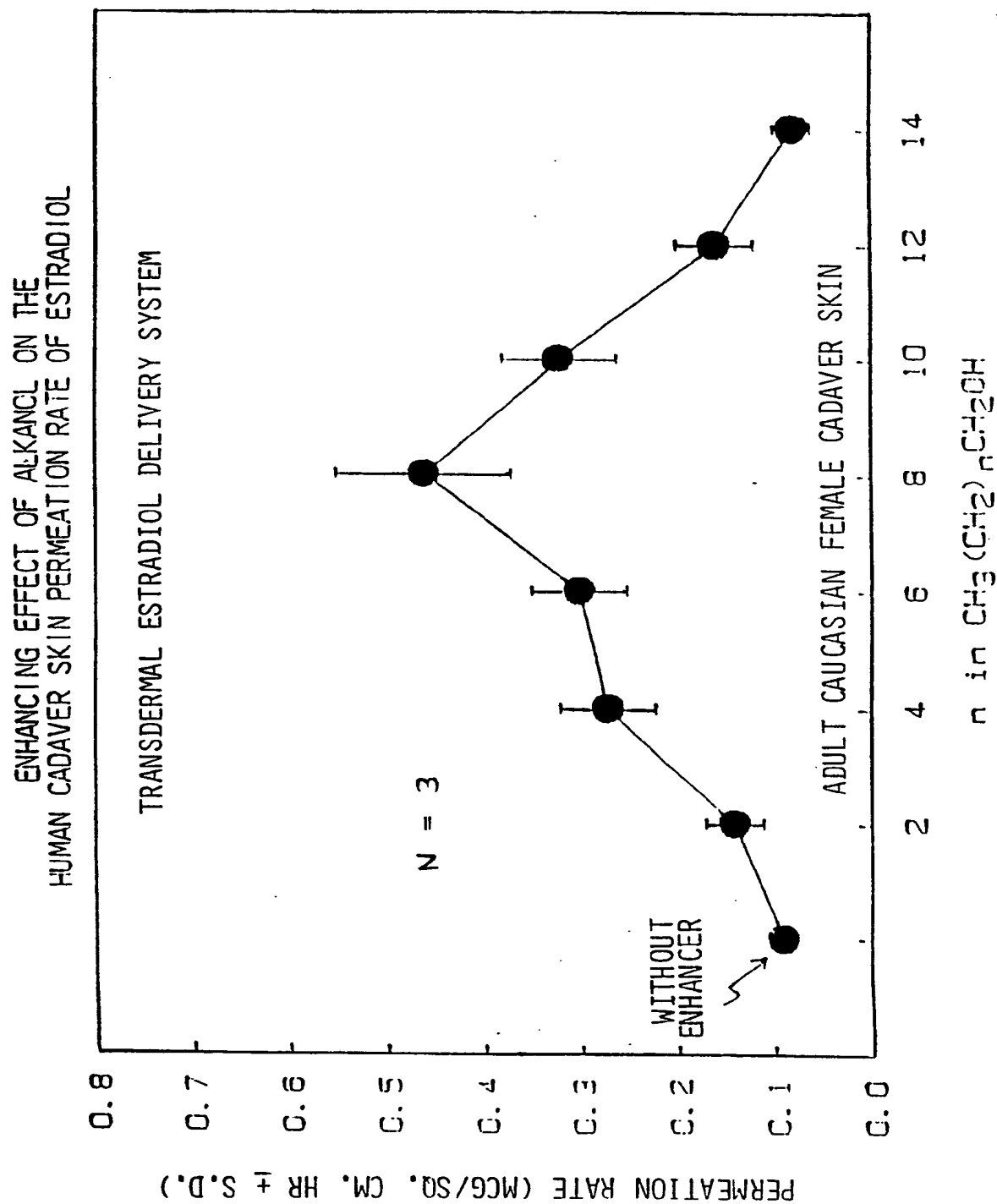
FIG. 1



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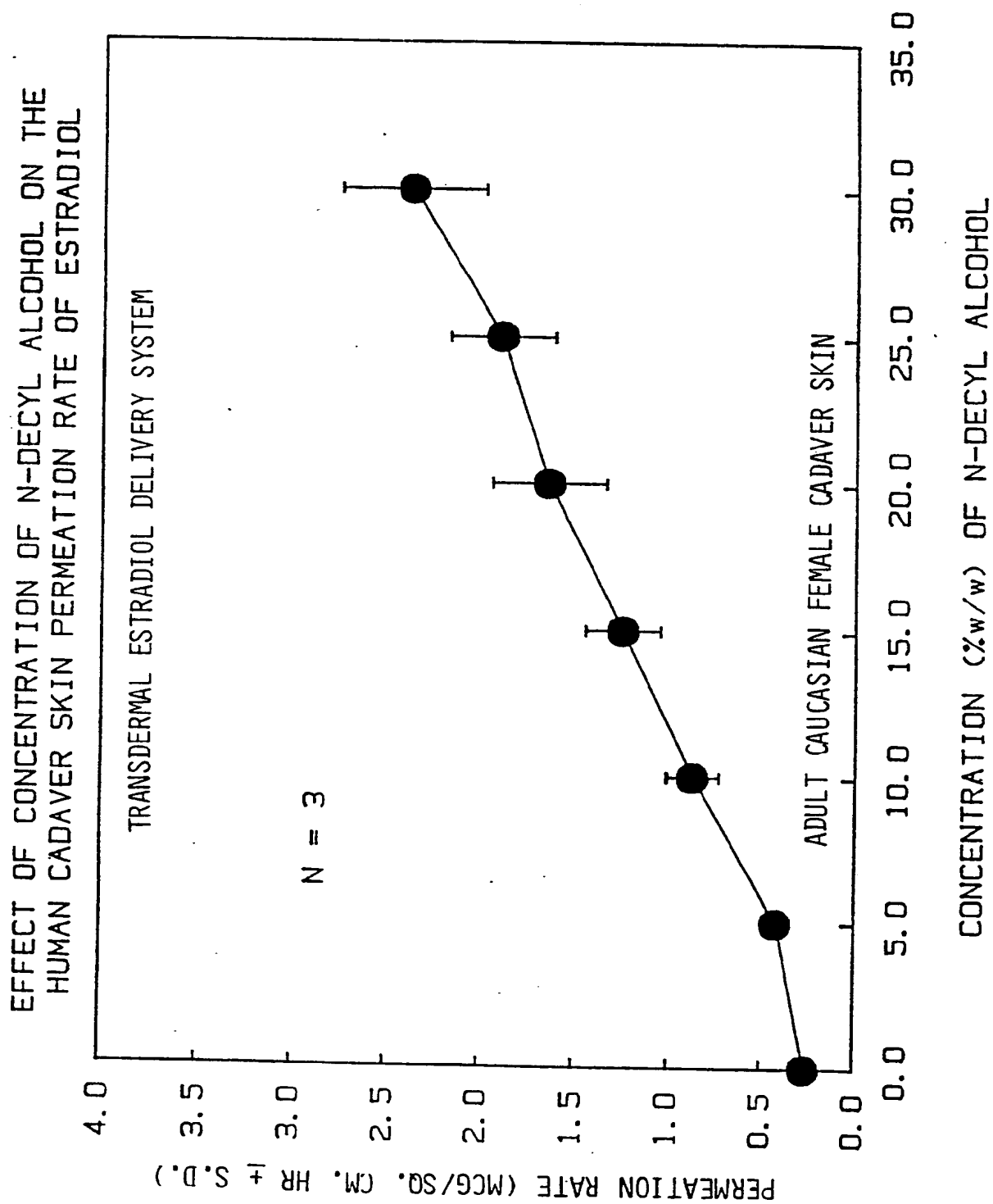
FIG. 2



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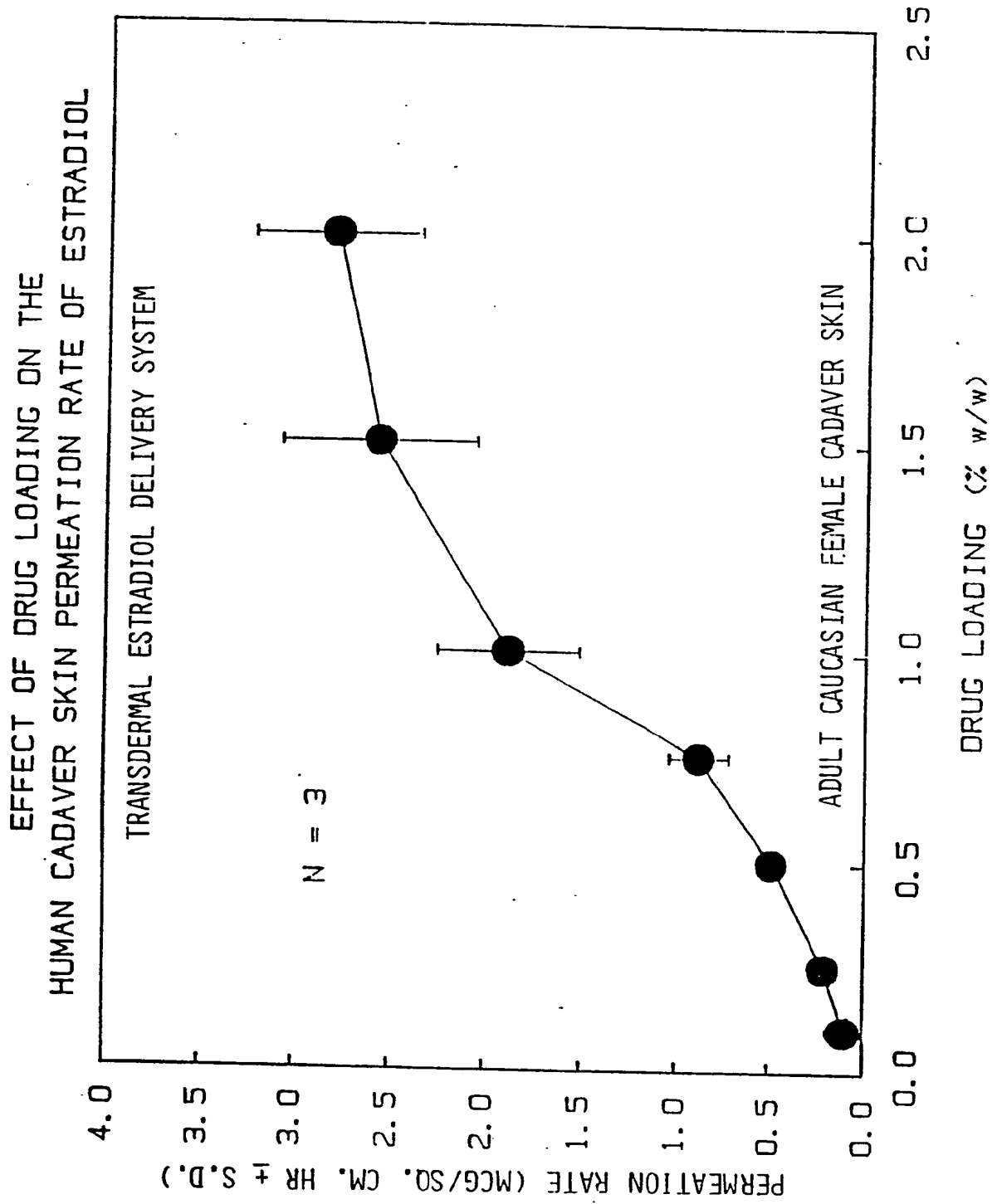
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FIG. 3

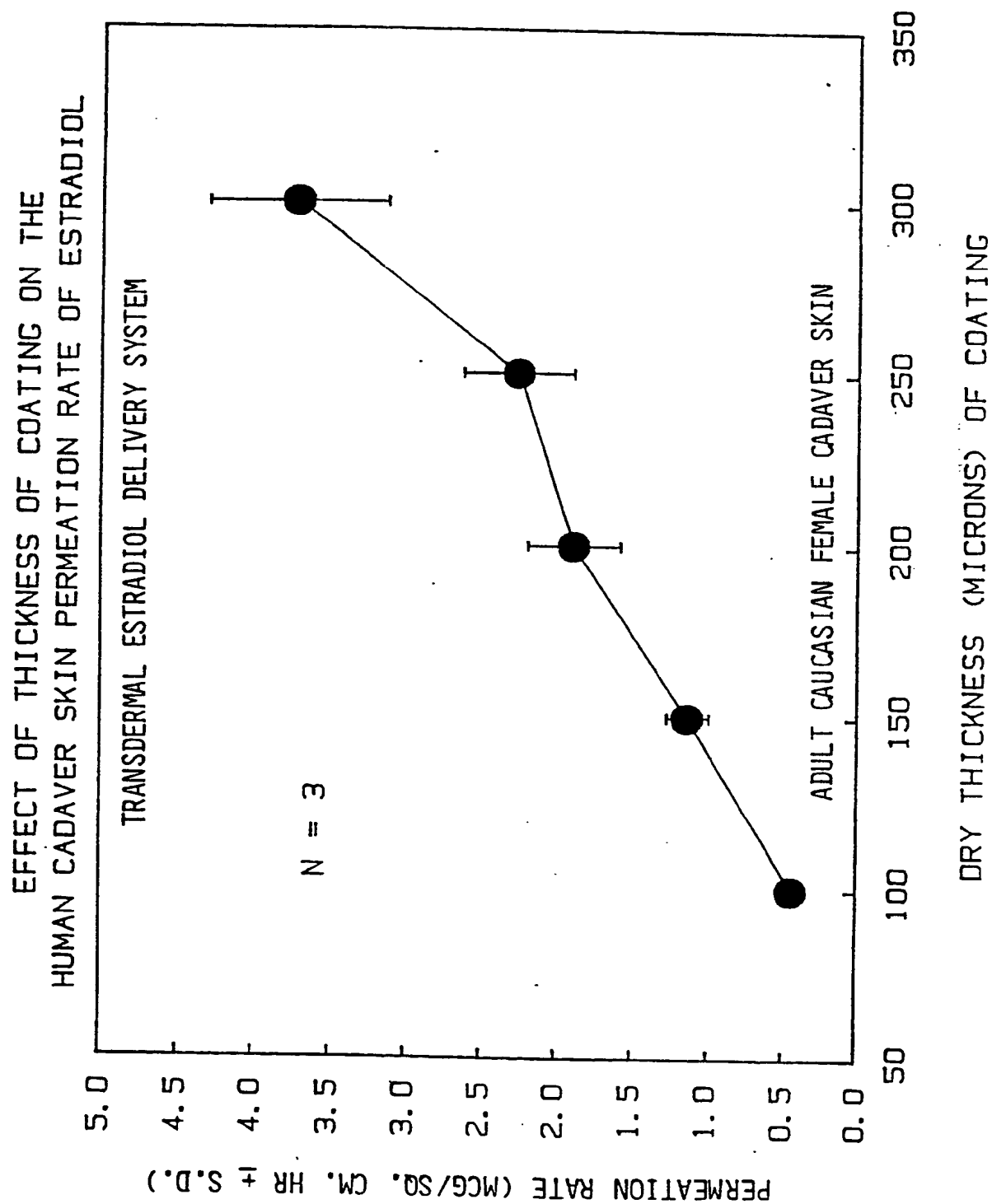


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FIG. 4



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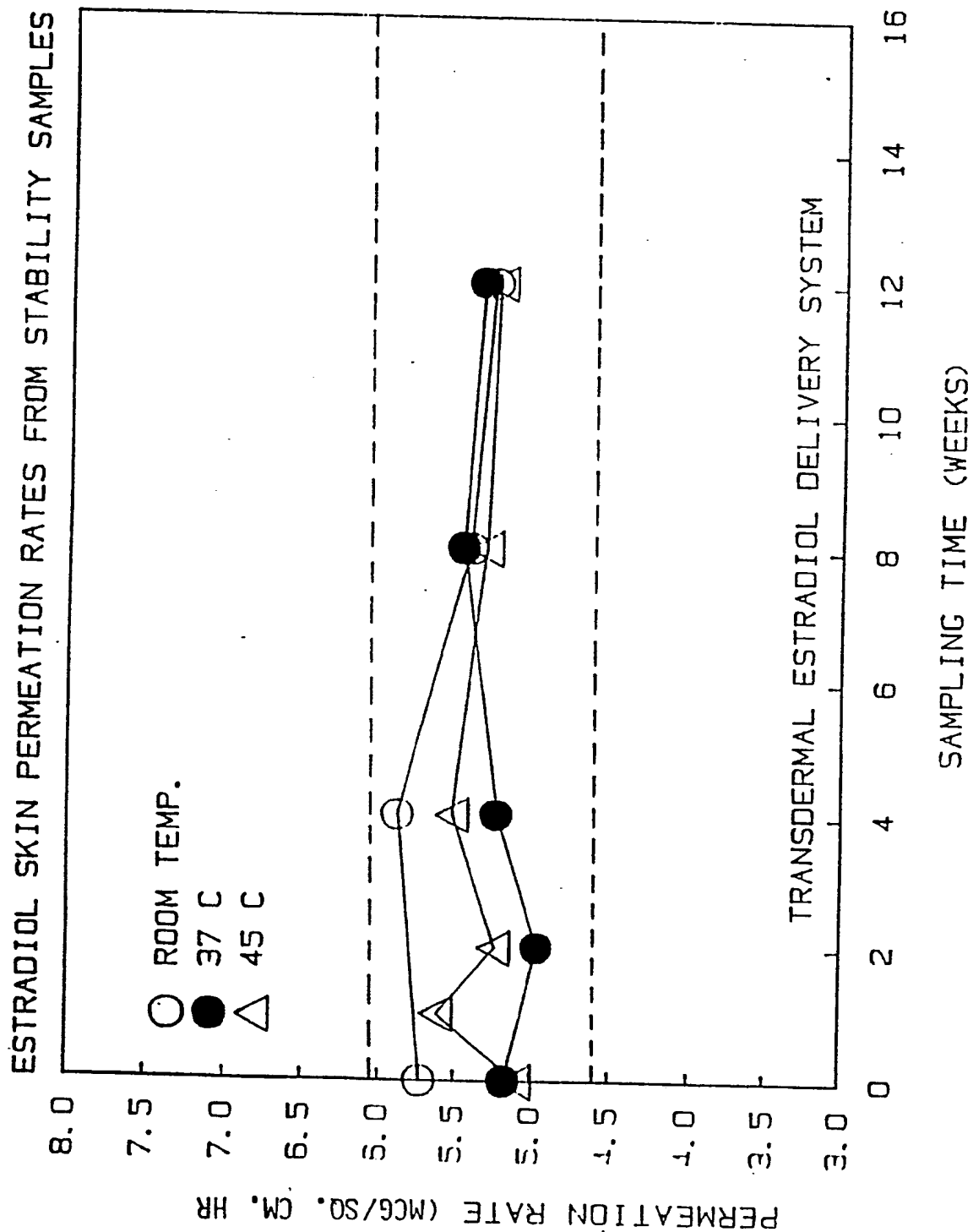
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FIG. 5

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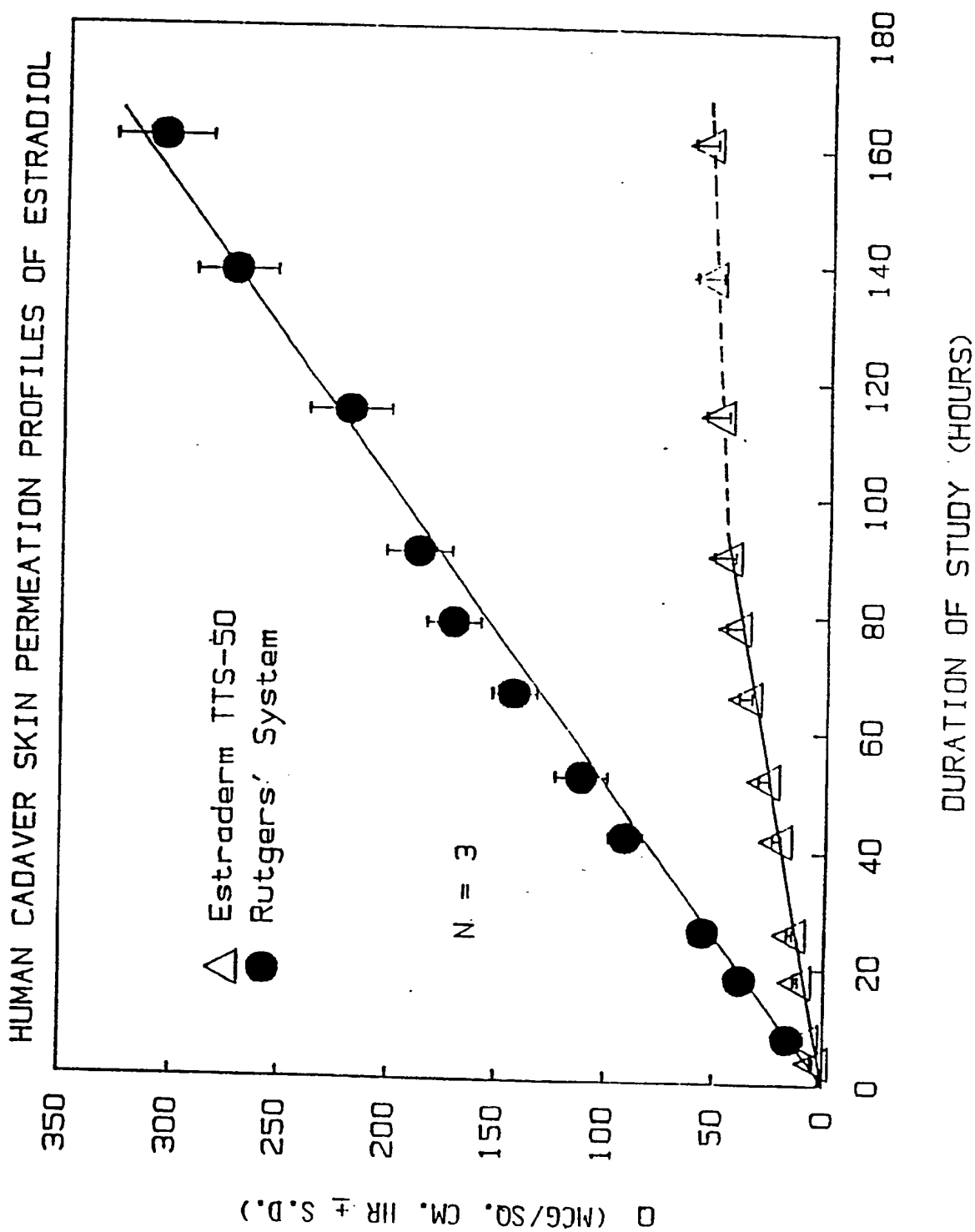
FIG. 6



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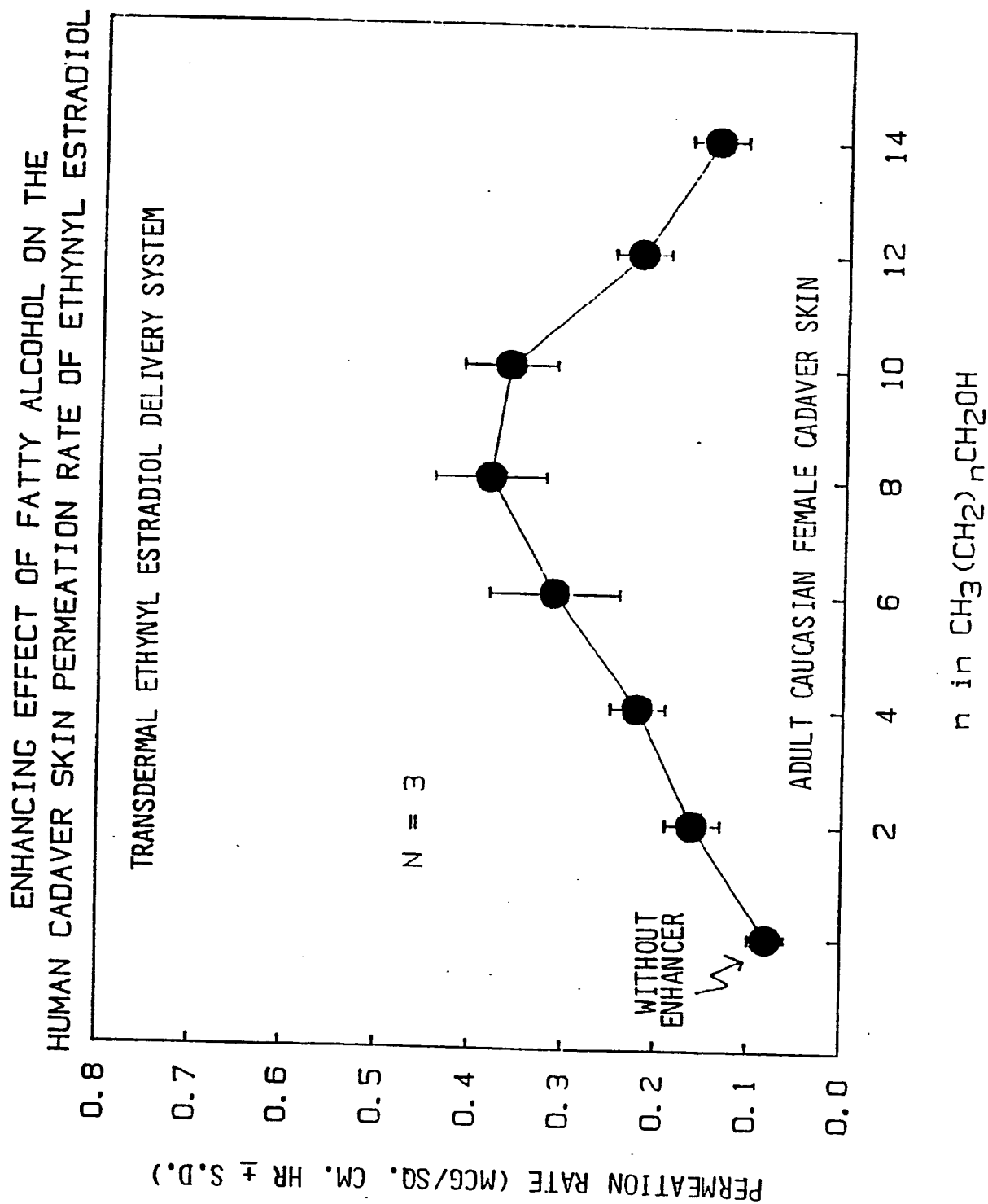
FIG. 7



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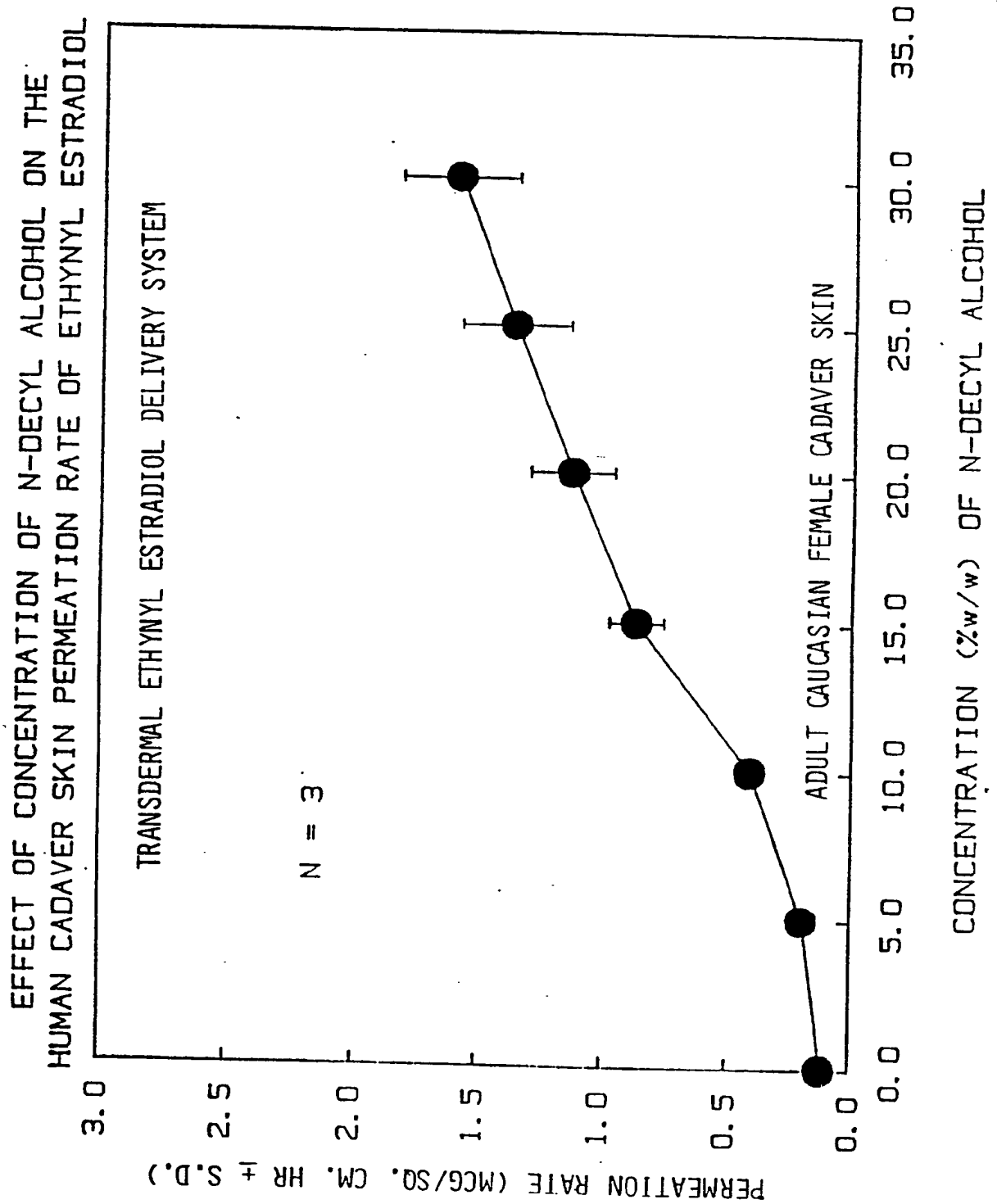
FIG. 8



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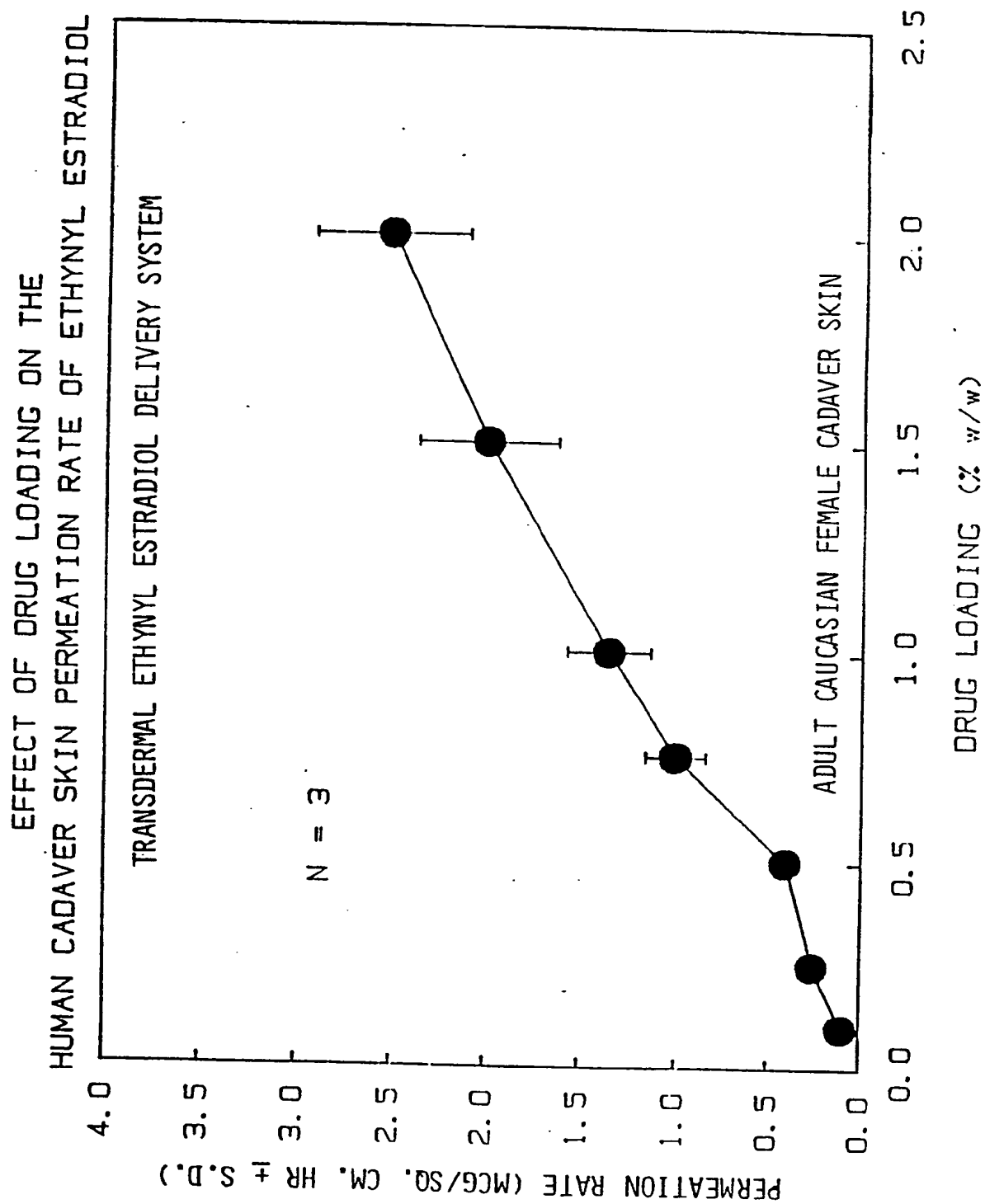
FIG. 9



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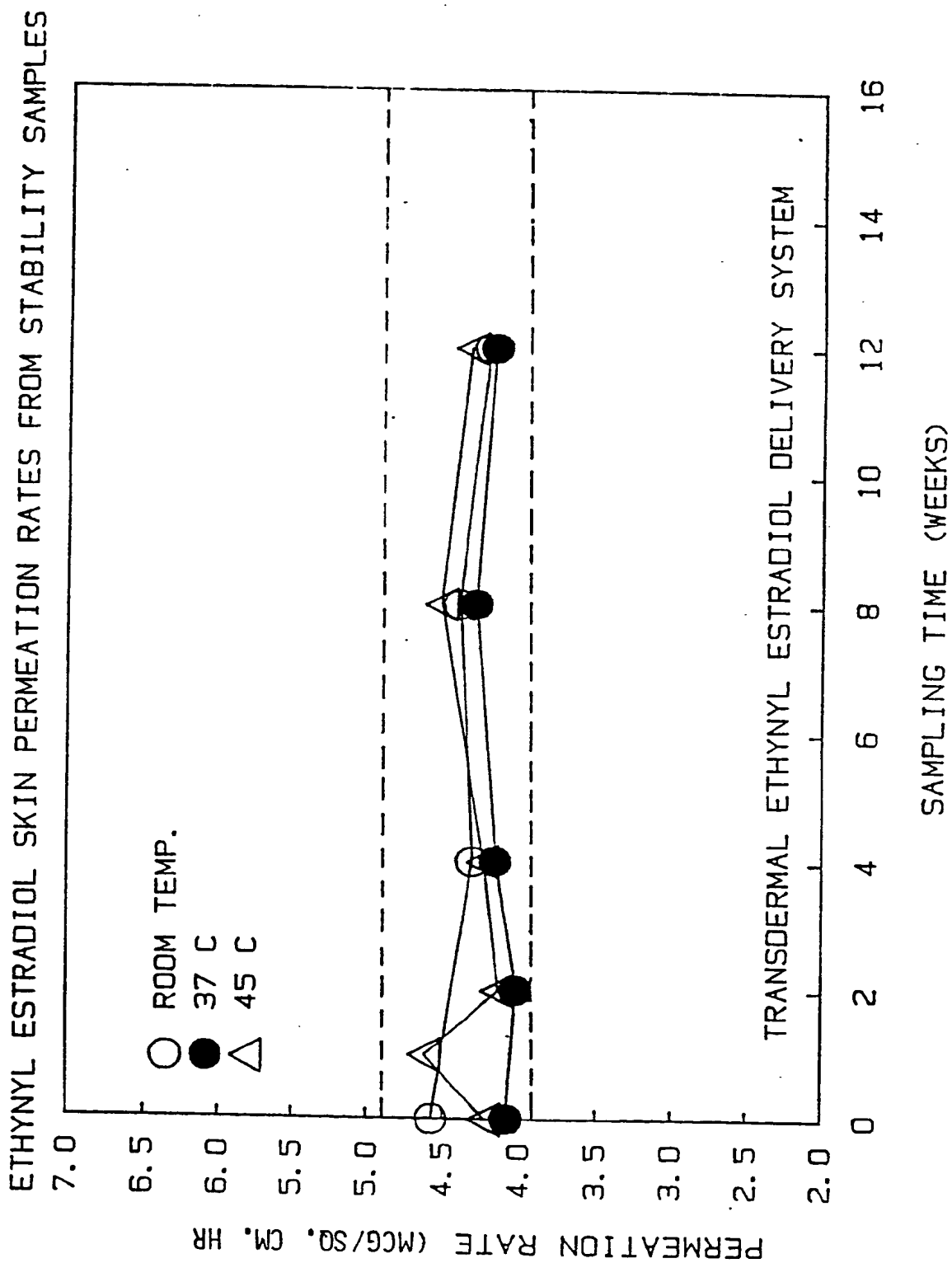
FIG. 10



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FIG. 11

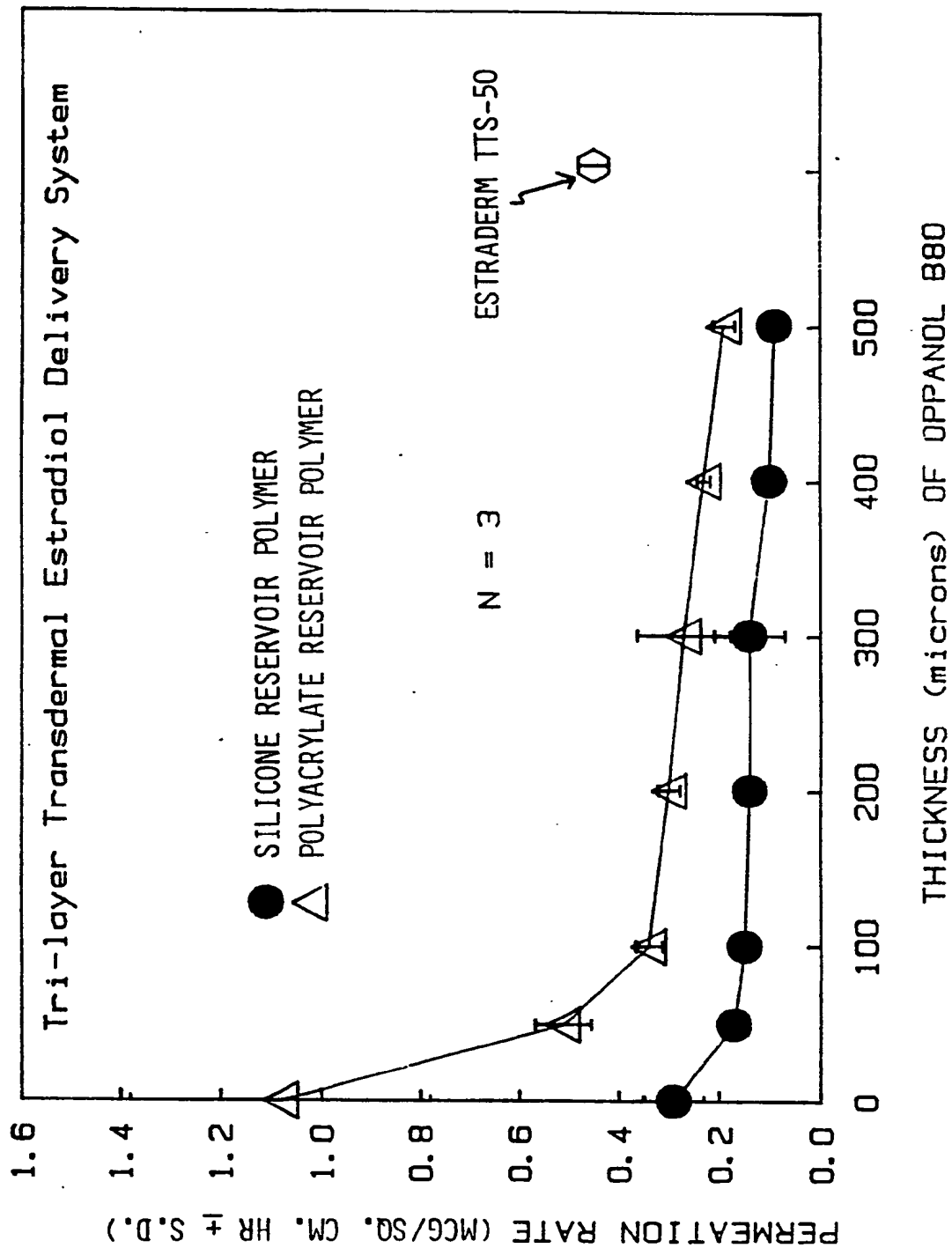


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FIG. 12

EFFECT OF THICKNESS OF OPPANOL B80 MIDDLE LAYER  
ON THE HUMAN CADAVER SKIN PERMEATION RATE OF ESTRADIOL

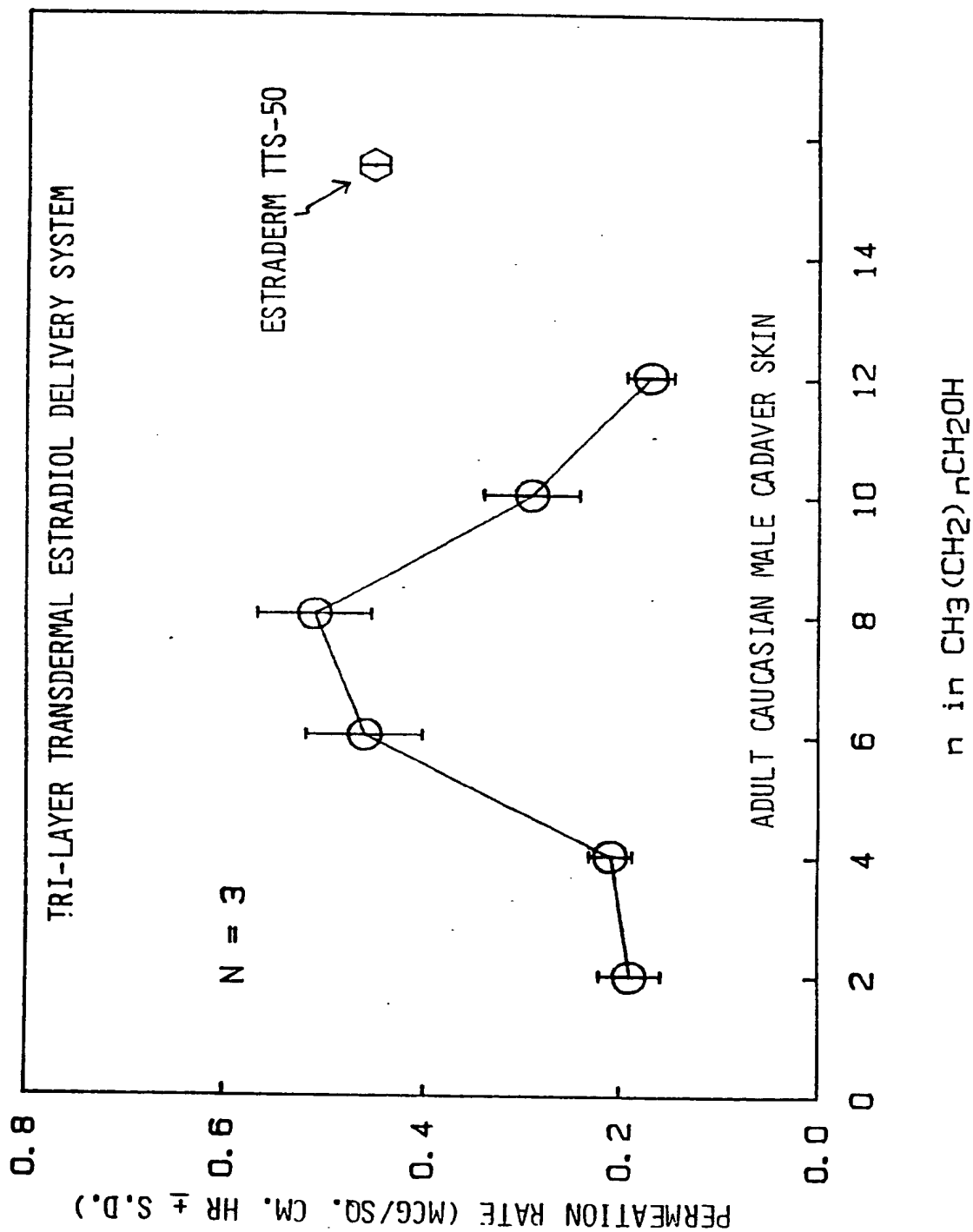


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FIG. 13

EFFECT OF CHAIN LENGTH OF FATTY ALCOHOLS AS ENHANCER  
ON THE HUMAN CADAVER SKIN PERMEATION RATE OF ESTRADIOL

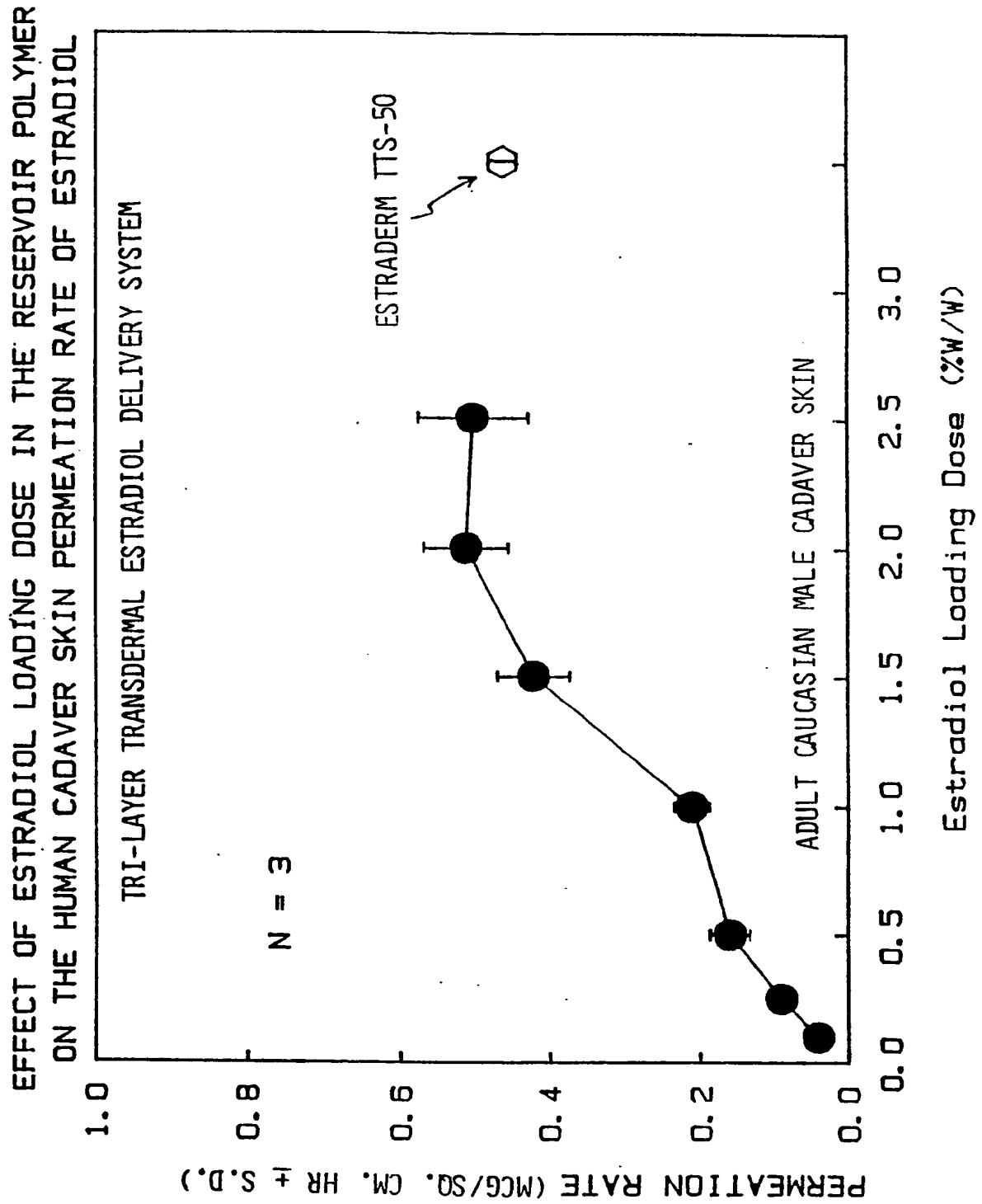


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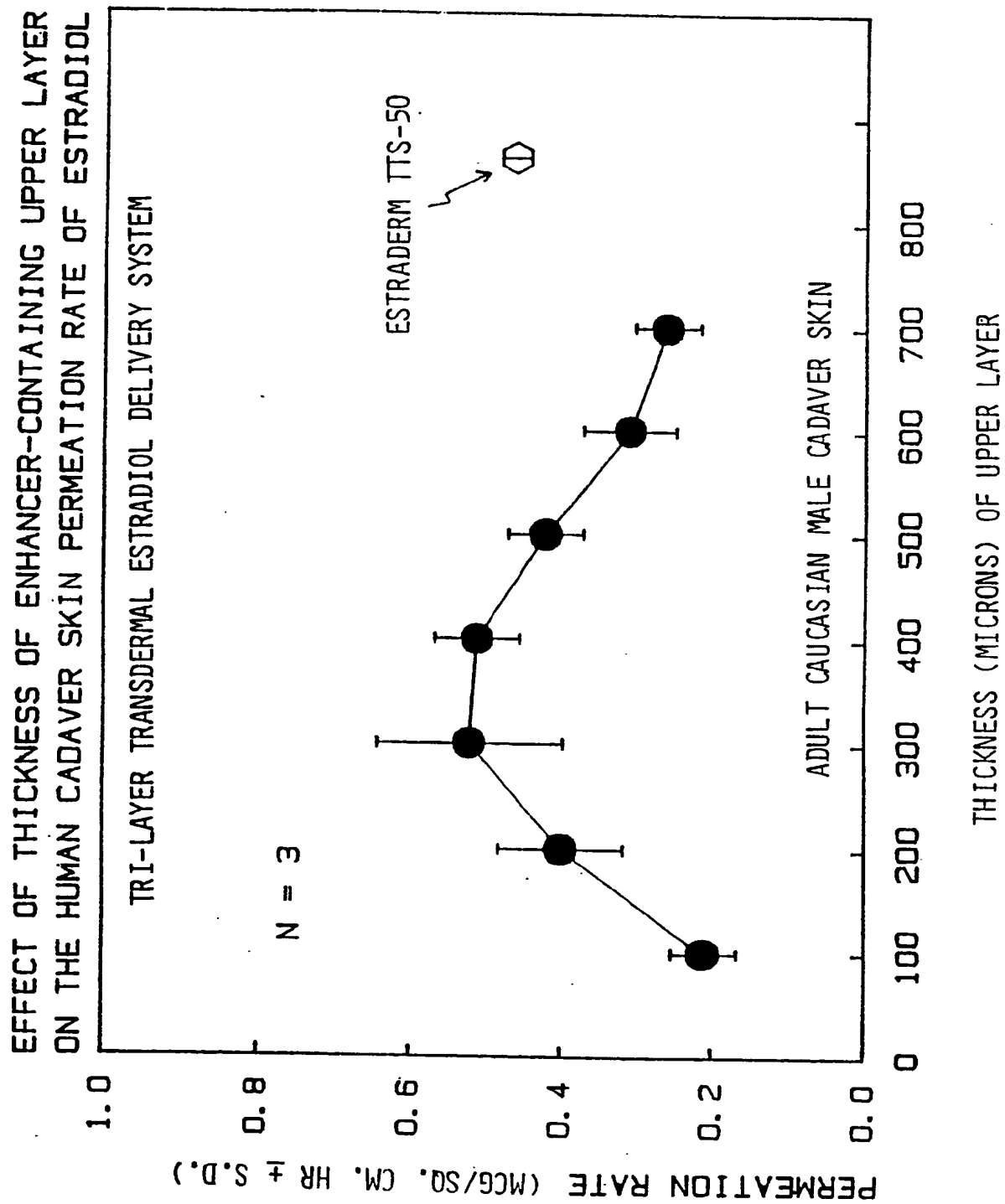
FIG. 14



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FIG. 15

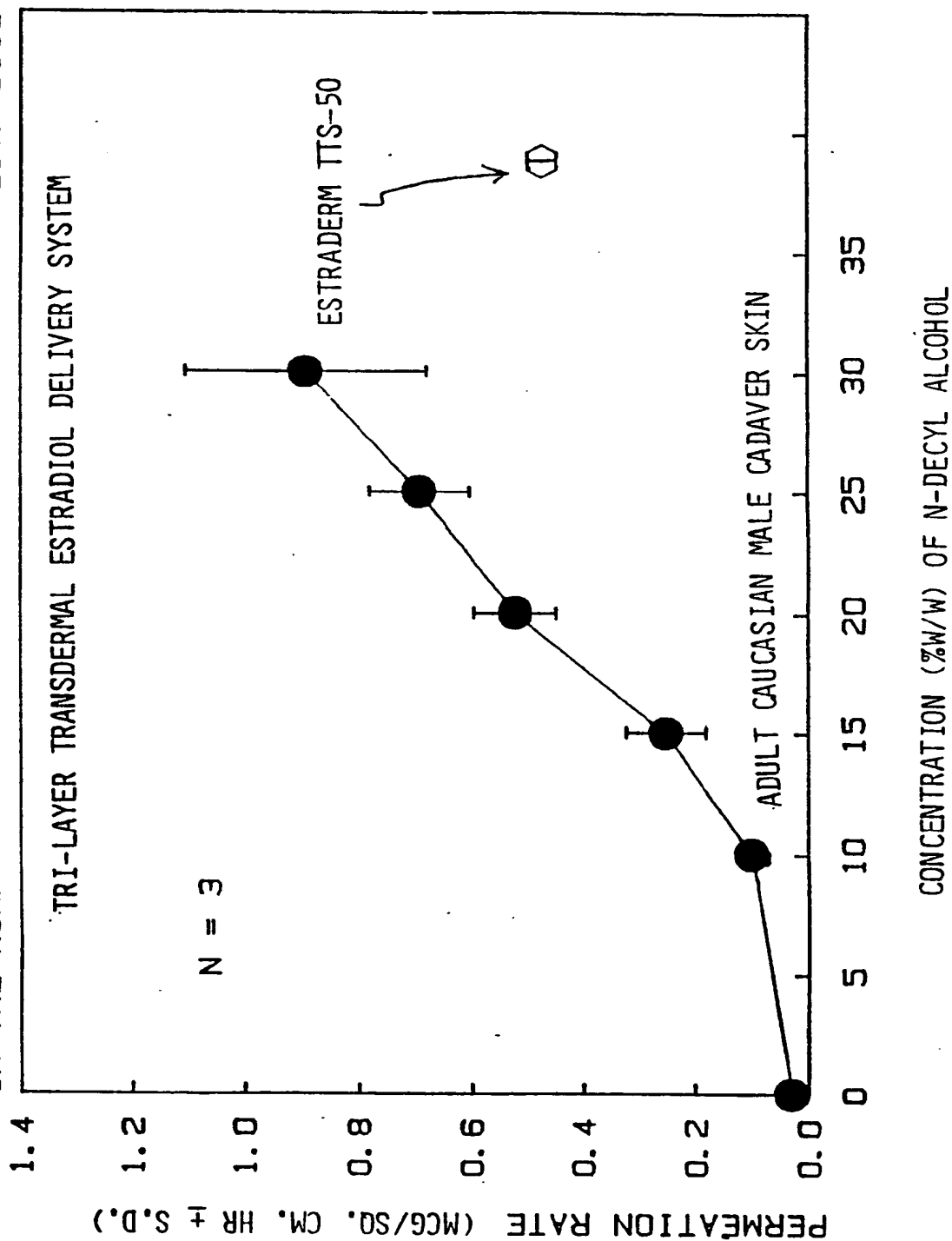


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FIG. 16

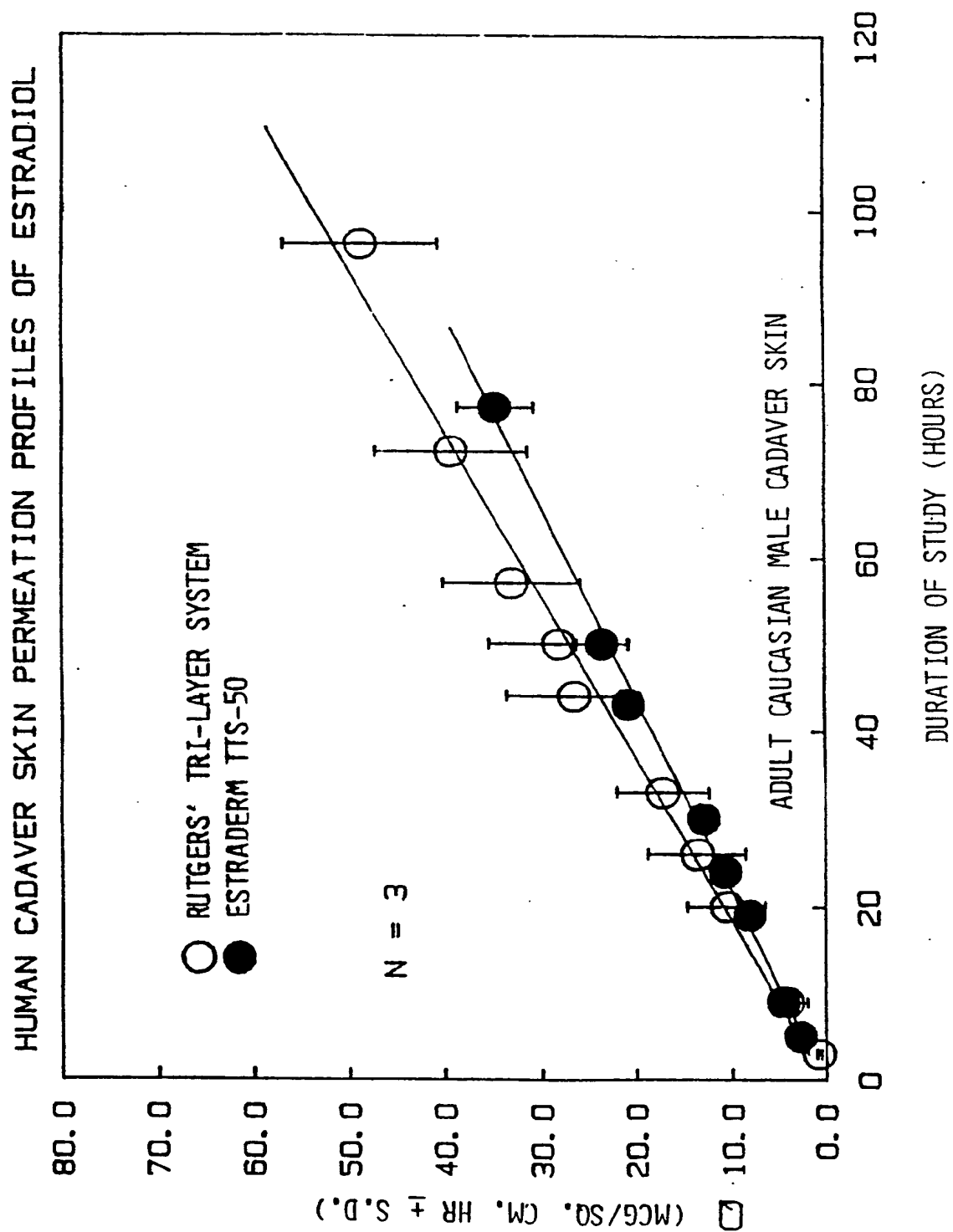
EFFECT OF CONCENTRATION OF n-DECYL ALCOHOL IN THE UPPER LAYER  
ON THE HUMAN CADAVER SKIN PERMEATION RATE OF ESTRADIOL



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FIG. 17



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# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US90/01273

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC<sup>5</sup> A 61F 13/02

U S Cl : 424/448

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System

Classification Symbols

U S Cl

424/448,449

Documentation Searched other than Minimum Documentation  
to the extent that such Documents are included in the Fields Searched

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of Document, " with indication, where appropriate, of the relevant passages *	Relevant to Claim No. *
X,P	US, A, 4,834,978 (NUWAYSER) 30 May 1989 see abstract and col. 2, lines 59, bridging top col. 3	1-20
X	US, A, 4,624,665 (NUWAYSER) 25 November 1986 see abstract, col. 1, li- col. 2, l 50	1-20
X	US, A, 4,687,481 (NUWAYSER) 18 August 1987- see abstract; col. 1, li - col. 2, l 50	1-20

### \* Special categories of cited documents: \*

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

26 April 1990

**09 JUL 1990**

International Searching Authority

Signature of Authorized Officer

ISA/US

Leon Horne

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